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<b>(54) Title:</b> HUMAN CANCER ASSOCIATED GENE SEQUENCES AND POLYPEPTIDES  <b>(57) Abstract</b>  This invention relates to newly identified tissue specific cancer associated polynucleotides and the polypeptides encoded by these polynucleotides herein collectively known as "cancer antigens", and to the complete gene sequences associated therewith and to the expression products thereof, as well as the use of such tissue specific cancer antigens for detection, prevention and treatment of tissue specific disorders, particularly the presence of cancer. This invention relates to the cancer antigens as well as vectors, host cells, antibodies directed to cancer antigens and recombinant and synthetic methods for producing the same. Also provided are diagnostic methods for diagnosing and treating, preventing and/or prognosing tissue specific disorders, including cancer, and therapeutic methods for treating such disorders. The invention further relates to screening methods for identifying agonists and antagonists of cancer antigens of the invention. The present invention further relates to methods and/or compositions for inhibiting the production and/or function of the polypeptides of the present invention.		

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## Human Cancer Associated Gene Sequences and Polypeptides

### 5    *Field of the Invention*

      This invention relates to newly identified tissue specific cancer associated polynucleotides and the polypeptides encoded by these polynucleotides herein collectively known as "cancer antigens," and to the complete gene sequences associated therewith and to the expression products thereof, as well as the use of such cancer antigens for detection,  
10    prevention and treatment of tissue specific diseases, particularly cancers. This invention relates to the cancer antigens as well as vectors, host cells, antibodies directed to cancer antigens and recombinant and synthetic methods for producing the same. Also provided are diagnostic methods for diagnosing and treating, preventing and/or prognosing disorders related to tissue specific diseases, including cancer, and therapeutic methods for treating such  
15    disorders. The invention further relates to screening methods for identifying agonists and antagonists of cancer antigens of the invention. The present invention further relates to methods and/or compositions for inhibiting the production and/or function of the polypeptides of the present invention.

### 20   *Background of the Invention*

      Cell growth is a carefully regulated process which responds to specific needs of the body. Occasionally, the intricate, and highly regulated controls dictating the rules for cellular division break down. When this occurs, the cell begins to grow and divide independently of its homeostatic regulation resulting in a condition commonly referred to as  
25    cancer. In fact, cancer is the second leading cause of death among Americans aged 25-44.

      Cancers or malignant tumors are characterized by continuous cell proliferation and cell death. Cancer cells have been shown to exhibit unique gene expression, and dozens of cancer-specific genetic markers, tumor antigens, have been identified. P35B, a tumor rejection antigen, was first identified in mouse. A point mutation in the P35B gene elicits a  
30    cytolytic T lymphocyte response but no detectable antibody response (Szikora, J. P. et al. (1990) EMBO J. 9:1041-1050). A human homolog of P35B, FX, is a homodimeric

NADP(H)-binding protein of 68 kDa. FX acts as a combined epimerase and NADPH-dependent reductase in converting GDP-4-keto-6-D-deoxymannose to GDP-L-fucose (Tonetti, M. et al. (1996) J. Biol. Chem. 271: 27274-27279). GDP-L-fucose is the substrate of several fucosyl-transferases involved in the biosynthesis of blood group ABH antigenic determinants. GDP-L-fucose is also utilized in synthesizing fucosylated glycoproteins and glycolipids which function in cell adhesion and recognition (Springer, T. A. and Lasky, L. A. (1991) Nature 329: 196-197; Brandley, B. K. et al. (1990) Cell 63: 861-863; and Feizi, T. and Childs, R. A. (1987) Biochem. J. 245: 1-11).

Thus, there is a need for the identification and characterization of novel tissue specific polynucleotides and polypeptides which modulate activation and differentiation of cells, both normally and in disease states. In particular, there is a need to isolate and characterize additional molecules that mediate apoptosis, DNA repair, tumor-mediated angiogenesis, genetic imprinting, immune responses to tumors and tumor antigens and, among other things, that can play a role in detecting, preventing, ameliorating or correcting dysfunctions or diseases.

### ***Summary of the Invention***

The present invention includes isolated nucleic acid molecules comprising, or alternatively, consisting of, a cancer associated polynucleotide sequence disclosed in the sequence listing (as SEQ ID NOs: 1 to 842) and/or contained in a human cDNA clone described in Tables 1, 2 and 5 and deposited with the American Type Culture Collection ("ATCC"). Fragments, variant, and derivatives of these nucleic acid molecules are also encompassed by the invention. The present invention also includes isolated nucleic acid molecules comprising, or alternatively consisting of, a polynucleotide encoding a cancer polypeptide. The present invention further includes cancer polypeptides encoded by these polynucleotides. Further provided for are amino acid sequences comprising, or alternatively consisting of, cancer polypeptides as disclosed in the sequence listing (as SEQ ID Nos: 843 to 1684) and/or encoded by a human cDNA clone described in Tables 1, 2 and 5 and deposited with the ATCC. Antibodies that bind these polypeptides are also encompassed by the invention. Polypeptide fragments, variants, and derivatives of these amino acid sequences are also encompassed by the invention, as are polynucleotides encoding these polypeptides and antibodies that bind these polypeptides. Also provided are diagnostic methods for diagnosing

and treating, preventing, and/or prognosing disorders related to cancer, and therapeutic methods for treating such disorders. The invention further relates to screening methods for identifying agonists and antagonists of cancer antigens of the invention.

## 5 *Detailed Description*

### Tables

Table 1 summarizes some of the cancer antigens encompassed by the invention (including contig sequences (SEQ ID NO:X) and the cDNA clone related to the contig  
10 sequence) and further summarizes certain characteristics of the cancer polynucleotides and the polypeptides encoded thereby. The first column shows the "SEQ ID NO:" for each of the 842 cancer antigen polynucleotide sequences of the invention. The second column provides a unique "Sequence/Contig ID" identification for each cancer associated sequence. The third column, "Gene Name," and the fourth column, "Overlap," provide a putative identification  
15 of the gene based on the sequence similarity of its translation product to an amino acid sequence found in a publicly accessible gene database and the database accession no. for the database sequence having similarity, respectively. The fifth and sixth columns provide the location (nucleotide position nos. within the contig), "Start" and "End", in the polynucleotide sequence "SEQ ID NO:X" that delineate the preferred ORF shown in the sequence listing as  
20 SEQ ID NO:Y. The seventh and eighth columns provide the "% Identity" (percent identity) and "% Similarity" (percent similarity), respectively, observed between the aligned sequence segments of the translation product of SEQ ID NO:X and the database sequence. The ninth column provides a unique "Clone ID" for a cDNA clone related to each contig sequence. The tenth column shows the tissue in which each SEQ ID NO:X is predominantly expressed.

25 Table 2 summarizes ATCC Deposits, Deposit dates, and ATCC designation numbers of deposits made with the ATCC in connection with the present application.

Table 3 indicates public ESTs, of which at least one, two, three, four, five, ten, fifteen or more of any one or more of these public EST sequences are optionally excluded from certain embodiments of the invention.

30 Table 4 lists residues comprising antigenic epitopes of antigenic epitope-bearing fragments present in most of the cancer associated polynucleotides described in Table 1 as predicted by the inventors using the algorithm of Jameson and Wolf, (1988) Comp. Appl.

Biosci. 4:181-186. The Jameson-Wolf antigenic analysis was performed using the computer program PROTEAN (Version 3.11 for the Power MacIntosh, DNASTAR, Inc., 1228 South Park Street Madison, WI). Cancer associated polypeptides (e.g., SEQ ID NO:Y, polypeptides encoded by SEQ ID NO:X, or polypeptides encoded by the cDNA in the referenced cDNA clone) may possess one or more antigenic epitopes comprising residues described in Table 4. It will be appreciated that depending on the analytical criteria used to predict antigenic determinants, the exact address of the determinant may vary slightly. The residues and locations shown in column two of Table 4 correspond to the amino acid sequences for most cancer associated polypeptide sequence shown in the Sequence Listing.

Table 5 shows the cDNA libraries sequenced, and ATCC designation numbers and vector information relating to these cDNA libraries.

#### **Definitions**

The following definitions are provided to facilitate understanding of certain terms used throughout this specification.

In the present invention, "isolated" refers to material removed from its original environment (e.g., the natural environment if it is naturally occurring), and thus is altered "by the hand of man" from its natural state. For example, an isolated polynucleotide could be part of a vector or a composition of matter, or could be contained within a cell, and still be "isolated" because that vector, composition of matter, or particular cell is not the original environment of the polynucleotide. The term "isolated" does not refer to genomic or cDNA libraries, whole cell total or mRNA preparations, genomic DNA preparations (including those separated by electrophoresis and transferred onto blots), sheared whole cell genomic DNA preparations or other compositions where the art demonstrates no distinguishing features of the polynucleotide/sequences of the present invention.

As used herein, a "polynucleotide" refers to a molecule having a nucleic acid sequence contained in SEQ ID NO:X (as described in column 1 of Table 1) or the related cDNA clone (as described in column 9 of Table 1 and contained within a library deposited with the ATCC). For example, the polynucleotide can contain the nucleotide sequence of the full length cDNA sequence, including the 5' and 3' untranslated sequences, the coding region, as well as fragments, epitopes, domains, and variants of the nucleic acid sequence.

Moreover, as used herein, a "polypeptide" refers to a molecule having an amino acid sequence encoded by a polynucleotide of the invention as broadly defined (obviously excluding poly-Phenylalanine or poly-Lysine peptide sequences which result from translation of a polyA tail of a sequence corresponding to a cDNA).

5 In the present invention, "SEQ ID NO:X" was often generated by overlapping sequences contained in multiple clones (contig analysis). A representative clone containing all or most of the sequence for SEQ ID NO:X is deposited at Human Genome Sciences, Inc. (HGS) in a catalogued and archived library. As shown in column 9 of Table 1, each clone is identified by a cDNA Clone ID. Each Clone ID is unique to an individual clone and the  
10 Clone ID is all the information needed to retrieve a given clone from the HGS library. In addition to the individual cDNA clone deposits, most of the cDNA libraries from which the clones were derived were deposited at the American Type Culture Collection (hereinafter "ATCC"). Table 5 provides a list of the deposited cDNA libraries. One can use the Clone ID to determine the library source by reference to Tables 2 and 5. Table 5 lists the deposited  
15 cDNA libraries by name and links each library to an ATCC Deposit. Library names contain four characters, for example, "HTWE." The name of a cDNA clone ("Clone ID") isolated from that library begins with the same four characters, for example "HTWEP07". As mentioned below, Table 1 correlates the Clone ID names with SEQ ID NOs. Thus, starting with a SEQ ID NO, one can use Tables 1, 2 and 5 to determine the corresponding Clone ID,  
20 from which library it came and in which ATCC deposit the library is contained. Furthermore, it is possible to retrieve a given cDNA clone from the source library by techniques known in the art and described elsewhere herein. The ATCC is located at 10801 University Boulevard, Manassas, Virginia 20110-2209, USA. The ATCC deposits were made pursuant to the terms of the Budapest Treaty on the international recognition of the deposit of microorganisms for  
25 the purposes of patent procedure.

A "polynucleotide" of the present invention also includes those polynucleotides capable of hybridizing, under stringent hybridization conditions, to sequences contained in SEQ ID NO:X, or the complement thereof (e.g., the complement of any one, two, three, four, or more of the polynucleotide fragments described herein), and/or sequences contained in the  
30 related cDNA clone within a library deposited with the ATCC. "Stringent hybridization conditions" refers to an overnight incubation at 42 degree C in a solution comprising 50% formamide, 5x SSC (750 mM NaCl, 75 mM trisodium citrate), 50 mM sodium phosphate (pH

7.6), 5x Denhardt's solution, 10% dextran sulfate, and 20 µg/ml denatured, sheared salmon sperm DNA, followed by washing the filters in 0.1x SSC at about 65 degree C.

Also included within "polynucleotides" of the present invention are nucleic acid molecules that hybridize to the polynucleotides of the present invention at lower stringency hybridization conditions. Changes in the stringency of hybridization and signal detection are primarily accomplished through the manipulation of formamide concentration (lower percentages of formamide result in lowered stringency); salt conditions, or temperature. For example, lower stringency conditions include an overnight incubation at 37 degree C in a solution comprising 6X SSPE (20X SSPE = 3M NaCl; 0.2M NaH<sub>2</sub>PO<sub>4</sub>; 0.02M EDTA, pH 7.4), 0.5% SDS, 30% formamide, 100 ug/ml salmon sperm blocking DNA; followed by washes at 50 degree C with 1XSSPE, 0.1% SDS. In addition, to achieve even lower stringency, washes performed following stringent hybridization can be done at higher salt concentrations (e.g. 5X SSC).

Note that variations in the above conditions may be accomplished through the inclusion and/or substitution of alternate blocking reagents used to suppress background in hybridization experiments. Typical blocking reagents include Denhardt's reagent, BLOTTO, heparin, denatured salmon sperm DNA, and commercially available proprietary formulations. The inclusion of specific blocking reagents may require modification of the hybridization conditions described above, due to problems with compatibility.

Of course, a polynucleotide which hybridizes only to polyA<sup>+</sup> sequences (such as any 3' terminal polyA<sup>+</sup> tract of a cDNA shown in the sequence listing), or to a complementary stretch of T (or U) residues, would not be included in the definition of "polynucleotide," since such a polynucleotide would hybridize to any nucleic acid molecule containing a poly (A) stretch or the complement thereof (e.g., practically any double-stranded cDNA clone generated using oligo dT as a primer).

The polynucleotides of the present invention can be composed of any polyribonucleotide or polydeoxribonucleotide, which may be unmodified RNA or DNA or modified RNA or DNA. For example, polynucleotides can be composed of single- and double-stranded DNA, DNA that is a mixture of single- and double-stranded regions, single- and double-stranded RNA, and RNA that is mixture of single- and double-stranded regions, hybrid molecules comprising DNA and RNA that may be single-stranded or, more typically, double-stranded or a mixture of single- and double-stranded regions. In addition, the

polynucleotide can be composed of triple-stranded regions comprising RNA or DNA or both RNA and DNA. A polynucleotide may also contain one or more modified bases or DNA or RNA backbones modified for stability or for other reasons. "Modified" bases include, for example, tritylated bases and unusual bases such as inosine. A variety of modifications can be made to DNA and RNA; thus, "polynucleotide" embraces chemically, enzymatically, or metabolically modified forms.

In specific embodiments, the polynucleotides of the invention are at least 15, at least 30, at least 50, at least 100, at least 125, at least 500, or at least 1000 continuous nucleotides but are less than or equal to 300 kb, 200 kb, 100 kb, 50 kb, 15 kb, 10 kb, 7.5kb, 5 kb, 2.5 kb, 2.0 kb, or 1 kb, in length. In a further embodiment, polynucleotides of the invention comprise a portion of the coding sequences, as disclosed herein, but do not comprise all or a portion of any intron. In another embodiment, the polynucleotides comprising coding sequences do not contain coding sequences of a genomic flanking gene (i.e., 5' or 3' to the gene of interest in the genome). In other embodiments, the polynucleotides of the invention do not contain the coding sequence of more than 1000, 500, 250, 100, 50, 25, 20, 15, 10, 5, 4, 3, 2, or 1 genomic flanking gene(s).

"SEQ ID NO:X" refers to a tissue specific cancer antigen polynucleotide sequence described in Table 1. SEQ ID NO:X is identified by an integer specified in column 1 of Table 1. The polypeptide sequence SEQ ID NO:Y is a translated open reading frame (ORF) encoded by polynucleotide SEQ ID NO:X. There are 842 cancer antigen polynucleotide sequences described in Table 1 and shown in the sequence listing (SEQ ID NO:1 through SEQ ID NO:842). Likewise there are 842 polypeptide sequences shown in the sequence listing, one polypeptide sequence for each of the polynucleotide sequences (SEQ ID NO:843 through SEQ ID NO:1684). The polynucleotide sequences are shown in the sequence listing immediately followed by all of the polypeptide sequences. Thus, a polypeptide sequence corresponding to polynucleotide sequence SEQ ID NO:1 is the first polypeptide sequence shown in the sequence listing. The second polypeptide sequence corresponds to the polynucleotide sequence shown as SEQ ID NO:2, and so on. In otherwords, since there are 842 polynucleotide sequences, for any polynucleotide sequence SEQ ID NO:X, a corresponding polypeptide SEQ ID NO:Y can be determined by the formula  $X + 842 = Y$ . In addition, any of the unique "Sequence/Contig ID" defined in column 2 of Table 1, can be linked to the corresponding polypeptide SEQ ID NO:Y by reference to Table 4.

The polypeptides of the present invention can be composed of amino acids joined to each other by peptide bonds or modified peptide bonds, i.e., peptide isosteres, and may contain amino acids other than the 20 gene-encoded amino acids. The polypeptides may be modified by either natural processes, such as posttranslational processing, or by chemical modification techniques which are well known in the art. Such modifications are well described in basic texts and in more detailed monographs, as well as in a voluminous research literature. Modifications can occur anywhere in a polypeptide, including the peptide backbone, the amino acid side-chains and the amino or carboxyl termini. It will be appreciated that the same type of modification may be present in the same or varying degrees at several sites in a given polypeptide. Also, a given polypeptide may contain many types of modifications. Polypeptides may be branched, for example, as a result of ubiquitination, and they may be cyclic, with or without branching. Cyclic, branched, and branched cyclic polypeptides may result from posttranslation natural processes or may be made by synthetic methods. Modifications include acetylation, acylation, ADP-ribosylation, amidation, covalent attachment of flavin, covalent attachment of a heme moiety, covalent attachment of a nucleotide or nucleotide derivative, covalent attachment of a lipid or lipid derivative, covalent attachment of phosphatidylinositol, cross-linking, cyclization, disulfide bond formation, demethylation, formation of covalent cross-links, formation of cysteine, formation of pyroglutamate, formylation, gamma-carboxylation, glycosylation, GPI anchor formation, hydroxylation, iodination, methylation, myristoylation, oxidation, pegylation, proteolytic processing, phosphorylation, prenylation, racemization, selenoylation, sulfation, transfer-RNA mediated addition of amino acids to proteins such as arginylation, and ubiquitination. (See, for instance, *PROTEINS - STRUCTURE AND MOLECULAR PROPERTIES*, 2nd Ed., T. E. Creighton, W. H. Freeman and Company, New York (1993); *POSTTRANSLATIONAL COVALENT MODIFICATION OF PROTEINS*, B. C. Johnson, Ed., Academic Press, New York, pgs. 1-12 (1983); Seifter et al., *Meth Enzymol* 182:626-646 (1990); Rattan et al., *Ann NY Acad Sci* 663:48-62 (1992).)

The cancer polypeptides of the invention can be prepared in any suitable manner. Such polypeptides include isolated naturally occurring polypeptides, recombinantly produced polypeptides, synthetically produced polypeptides, or polypeptides produced by a combination of these methods. Means for preparing such polypeptides are well understood in the art.



The polypeptides may be in the form of the secreted protein, including the mature form, or may be a part of a larger protein, such as a fusion protein (see below). It is often advantageous to include an additional amino acid sequence which contains secretory or leader sequences, pro-sequences, sequences which aid in purification, such as multiple  
5 histidine residues, or an additional sequence for stability during recombinant production.

The cancer polypeptides of the present invention are preferably provided in an isolated form, and preferably are substantially purified. A recombinantly produced version of a polypeptide, including the secreted polypeptide, can be substantially purified using techniques described herein or otherwise known in the art, such as, for example, by the one-  
10 step method described in Smith and Johnson, Gene 67:31-40 (1988). Polypeptides of the invention also can be purified from natural, synthetic or recombinant sources using techniques described herein or otherwise known in the art, such as, for example, antibodies of the invention raised against the polypeptides of the present invention in methods which are well known in the art.

15 By a polypeptide demonstrating a "functional activity" is meant, a polypeptide capable of displaying one or more known functional activities associated with a full-length (complete) protein of the invention. Such functional activities include, but are not limited to, biological activity, antigenicity [ability to bind (or compete with a polypeptide for binding) to an anti-polypeptide antibody], immunogenicity (ability to generate antibody which binds to  
20 a specific polypeptide of the invention), ability to form multimers with polypeptides of the invention, and ability to bind to a receptor or ligand for a polypeptide.

"A polypeptide having functional activity" refers to polypeptides exhibiting activity similar, but not necessarily identical to, an activity of a polypeptide of the present invention, including mature forms, as measured in a particular assay, such as, for example, a biological  
25 assay, with or without dose dependency. In the case where dose dependency does exist, it need not be identical to that of the polypeptide, but rather substantially similar to the dose-dependence in a given activity as compared to the polypeptide of the present invention (i.e., the candidate polypeptide will exhibit greater activity or not more than about 25-fold less  
and, preferably, not more than about tenfold less activity, and most preferably, not more than  
30 about three-fold less activity relative to the polypeptide of the present invention).

The functional activity of the cancer antigen polypeptides, and fragments, variants derivatives, and analogs thereof, can be assayed by various methods.

For example, in one embodiment where one is assaying for the ability to bind or compete with full-length polypeptide of the present invention for binding to an antibody to the full length polypeptide antibody, various immunoassays known in the art can be used, including but not limited to, competitive and non-competitive assay systems using techniques  
5 such as radioimmunoassays, ELISA (enzyme linked immunosorbent assay), "sandwich" immunoassays, immunoradiometric assays, gel diffusion precipitation reactions, immunodiffusion assays, in situ immunoassays (using colloidal gold, enzyme or radioisotope labels, for example), western blots, precipitation reactions, agglutination assays (e.g., gel agglutination assays, hemagglutination assays), complement fixation assays,  
10 immunofluorescence assays, protein A assays, and immunoelectrophoresis assays, etc. In one embodiment, antibody binding is detected by detecting a label on the primary antibody. In another embodiment, the primary antibody is detected by detecting binding of a secondary antibody or reagent to the primary antibody. In a further embodiment, the secondary antibody is labeled. Many means are known in the art for detecting binding in an  
15 immunoassay and are within the scope of the present invention.

In another embodiment, where a ligand is identified, or the ability of a polypeptide fragment, variant or derivative of the invention to multimerize is being evaluated, binding can be assayed, e.g., by means well-known in the art, such as, for example, reducing and non-reducing gel chromatography, protein affinity chromatography, and affinity blotting. See  
20 generally, Phizicky, E., et al., Microbiol. Rev. 59:94-123 (1995). In another embodiment, physiological correlates polypeptide of the present invention binding to its substrates (signal transduction) can be assayed.

In addition, assays described herein (see Examples) and otherwise known in the art may routinely be applied to measure the ability of polypeptides of the present invention and  
25 fragments, variants derivatives and analogs thereof to elicit polypeptide related biological activity (either in vitro or in vivo). Other methods will be known to the skilled artisan and are within the scope of the invention.

### 30 **Cancer Associated Polynucleotides and Polypeptides of the Invention**

It has been discovered herein that the polynucleotides described in Table 1 are expressed at significantly enhanced levels in human cancer tissues as shown in column 10 of

Table 1. Accordingly, such polynucleotides, polypeptides encoded by such polynucleotides, and antibodies specific for such polypeptides find use in the prediction, diagnosis, prevention and treatment of tissue specific disorders, including cancer as more fully described below.

Table 1 summarizes some of the polynucleotides encompassed by the invention  
5 (including contig sequences (SEQ ID NO:X) and the related cDNA clones) and further summarizes certain characteristics of these tissue specific cancer associated polynucleotides and the polypeptides encoded thereby.

Table 1

Seq ID	Sequence/ Contig ID	Gene Name	Overlap	HGS Nucleotide Start End	% Identity	% Similarity	Clone ID	Tissue(s)
1	507291	uvomorulin [Homo sapiens] >sp Q15855 Q15855 UVOMORULIN PRECURSOR (F-CADHERIN) (ARC-14)UVOMORULIN). >gi 930046 uvomorulin (140 AA) [Homo sapiens] {SUB 168-307} Length = 878	gi 340185	2 475	100	100	HC1A123	Pancreas, Breast/Ovarian
2	508000	HLA-B-associated transcript 2 (BAT2) [Homo sapiens] >gi 179345 HLA-B-associated transcript 2 (BAT2) [Homo sapiens] >pir B35098 B35098 MHC class III histocompatibility antigen HLA-B- associated transcript 2 - human >sp P48634 BAT2_HUMAN LARGE PROLINE- RICH P	gi 179339	100 1902	86	87	HWAAK56	Lung, Breast/Ovarian
3	518325			110 310			HHFCP36	Lung, Pancreas, Colon, Breast/Ovarian
4	523111	Sm D2 [Homo sapiens] >pir 38861 38861 small nuclear ribonucleoprotein chain D2 - human Length = 118	gi 600748	233 670	88	88	HA1A67	Lung, Breast/Ovarian
5	526869	(AC002291) Similar ATP-dependent RNA Helicase [Arabidopsis thaliana] >sp O49289 O49289 SIMILAR ATP-DEPENDENT RNA HELICASE. Length = 845	gi 2829912	1 552	67	77	HT41P57	Pancreas, Breast/Ovarian
6	532211	retinoic acid-binding protein [Bos taurus] Length = 138	gi 162906	2 481	95	98	HHGC-V63	Lung, Breast/Ovarian

7	532247		160	384		HEBCC47	Pancreas, Breast/Ovarian Lung, Breast/Ovarian
8	537932	alcohol dehydrogenase [Homo sapiens] >gi178134 alcohol dehydrogenase 3 [Homo sapiens] >pir JH0789 DEHUC2 alcohol dehydrogenase (EC 1.1.1.1) 5 - human >sp P11766 ADHX_HUMAN ALCOHOL DEHYDROGENASE CLASS III CHI CHAIN (EC 1.1.1.1) (GLUTATHIONE- DEPENDENT FOR	gi178130	1	1149	92	HUSIB86
9	540117		174	635		HRGBU25	Lung, Breast/Ovarian
10	547710	transketolase [Homo sapiens] Length = 623	gi1297297	2	1189	92	HNICAZ27
11	551747	rtvp-1 [Homo sapiens] >pir JC5308 JC5308 testis- specific, vespid. and pathogenesis-related protein 1 - human >sp P48060 GLIP_HUMAN GLIOMA PATHOGENESIS-RELATED PROTEIN (RTVP-1 PROTEIN). Length = 266	gi1030053	26	931	91	HTDAE10
12	552799	delta- aminolevulinate synthase (housekeeping) [Homo sapiens] >pir S13682 SYHUAL 5- aminolevulinate synthase (EC 2.3.1.37) 1 precursor - human >sp P13196 HEM1_HUMAN 5- AMINOLEVULINIC ACID SYNTHASE MITOCHONDRIAL PRECURSOR. NONSPECIFIC (EC 2.3.1.37) (DELTA-AM	gi128583	104	814	100	HHLCX90

13	553243	RING7 [Homo sapiens] >gi 557702 HLA-DMB [Homo sapiens] >gi 512472 HLA-DMB [Homo sapiens] >gi 1054742 DMB [Homo sapiens] >pir 37533 37533 MHC class II histocompatibility antigen HLA-DM beta chain precursor - human Length = 263	gi 313002	202	1017	93	93	HUKDI44	Lung, Pancreas
14	553368	(AF053944) aortic carboxypeptidase-like protein ACLP [Homo sapiens] >sp G3288916 G3288916 AORTIC CARBOXYPEPTIDASE-LIKE PROTEIN ACLP >gn PID 1013781 AEBP1 [Homo sapiens]  SUB 314-1158  Length = 1158	gi 3288916	1	459	96	96	HADGE84	Lung, Pancreas
15	554349								
16	558491	immunoglobulin heavy chain [Homo sapiens] Length = 152	gi 567128	1	429	98	100	HUSGK19 HUFEN61	Lung, Pancreas Lung, Pancreas, Colon
17	558983	d16802.2 [Homo sapiens] >sp P35579 MYSN_HUMAN MYOSIN HEAVY CHAIN, NONMUSCLE TYPE A (CELLULAR MYOSIN HEAVY CHAIN, TYPE A) (NMIMIC-A). >gi 553596 cellular myosin heavy chain [Homo sapiens]  SUB 1-1337  Length = 1960	gn P1D e1294465	219	623	100	100	HC11BM82	Pancreas, Breast/Ovarian
18	572943			367	522			HBAMC47	Pancreas, Breast/Ovarian
19	585892	epithelial tumor antigen precursor, membrane-bound form - human Length = 515	pir S10572 S10572	3	965	89	89	HUKAL69	Lung, Pancreas, Colon, Breast/Ovarian

20	589390	C1 inhibitor [Homo sapiens] >gi 29535 C1 inhibitor [Homo sapiens] >pir S15386 THUC1 complement C1 inhibitor precursor - human >sp P05135 C1_HUMAN PLASMA PROTEASE C1 INHIBITOR PRECURSOR (C1 INH). >gnl P D c3783 C1 inhibitor (AA 155-478 ) (1 is 2nd base i	gnl P D e222400	3	983	96	96	HSRAB10	Lung, Pancreas
21	596882			800	1057			HMCEP91	Lung, Pancreas, Colon
22	616289	nucleoporin p58 [Rattus norvegicus] >sp P70581 P70581 NUCLEOPORIN P58. Length = 585	gi 1537068	1	390	67	70	H1AJCB44	Lung, Pancreas
23	622140	selenophosphate synthetase 2 [Homo sapiens] >sp Q99611 Q99611 SELENOPHOSPHATE SYNTHETASE 2. Length = 448	gi 1815622	92	323	97	97	HEONC67	Pancreas, Breast/Ovarian
24	623566	karyopherin alliph 3 [Homo sapiens] >sp O00505 JIMA3_HUMAN IMPORTIN ALPHA-3 SUBUNIT (KARYOPHERIN ALPHA-3 SUBUNIT). Length = 521	gnl P D d1021210	66	1652	99	99	HDPP20	Lung, Breast/Ovarian
25	647714			1	711			INSF129	Pancreas, Breast/Ovarian
26	647732	ubiquitin conjugating-protein [Oryctolagus cuniculus] >gi 184046 HHR6B (Human homologue of yeast RAD 6); putative [Homo sapiens] >gi 30954 E2 protein [Homo sapiens] >gi 207555 ubiquitin conjugating-protein [Rattus norvegicus] >gnl P D e233515 HR6B gene pr	gi 165780	3	590	100	100	HDTD146	Lung, Colon

27	651774	P58 [Homo sapiens] >pir[S68363]S68363 protein disulfide-isomerase (EC 5.3.4.1) ER60 precursor - human >sp[P30101]ER60_HUMAN PROBABLE PROTEIN DISULFIDE ISOMERASE ER-60 PRECURSOR (EC 5.3.4.1) (ERP60) (58 KD MICROSOMAL PROTEIN) (P58) (GRP58) (ERP57). Length	gil147739	1	1632	96	96	HDPAAL5	Lung, Pancreas, Breast/Ovarian
28	651995	collagen [Mus musculus] >pir[S23779]S23779 collagen alpha 1(VIII) chain - mouse >sp[Q00780]CA18_MOUSE COLLAGEN ALPHA 1(VIII) CHAIN PRECURSOR. >bhs[134935 alpha 1-VIII collagen [rats, mesangial cell, Peptide Partial, 172 aa] [Rattus sp.] (SUB 399-370) Leng	gilPIDlc245912	3	335	90	95	11B1A1344	Lung, Pancreas
29	652156	phospholipid hydroperoxide glutathione peroxidase [Homo sapiens] >sp[Q43381]Q43381 GSHH_HUMAN (EC 1.1.1.9) (GLUTATHIONE PEROXIDASE). >gil3399677 (AC005390) GSSH_HUMAN, partial CDS [Homo sapiens] (SUB 149-197) Length = 197	gil825667	262	633	94	94	HOEBK80	Lung, Breast/Ovarian
30	653010	von Willebrand factor [Homo sapiens]		79	183			HSRAA58	Lung, Pancreas
31	655904	>pir[A34480]VWHU von Willebrand factor precursor - human >gil553810 von Willebrand factor [Homo sapiens] (SUB 990-1947) >gilPIDlc222518 von Willebrand factor [Homo sapiens] (SUB 1-178) >gil340316 von Willebrand antigen	gil340356	632	1891	96	96	HSBIB94	Lung, Breast/Ovarian
32	657852			70	522			HCHAL14	Colon, Breast/Ovarian
33	666414			1	285			HOSEFC18	Lung, Pancreas



34	667847	ribosomal protein S9 [Rattus norvegicus] >pir N0587 S21497 ribosomal protein S9 - rat Length = 194	gi 57143	1	714	98	98	HICL162	Lung, Pancreas, Breast/Ovarian
35	670188	G protein gamma-10 subunit [Homo sapiens] >pir J9158 J9158 GTP-binding regulatory protein gamma-10 chain - human >sp P50151 GBGA_HUMAN GUANINE NUCLEOTIDE-BINDING PROTEIN G(I)/G(S)/G(O) GAMMA-10 SUBUNIT. Length = 68	gi 995919	2	238	100	100	HWADR30	Lung, Pancreas
36	670279	ribosomal protein S24 [Homo sapiens] >gi 517222 ribosomal protein S24 [Homo sapiens] >gi 49652 ribosomal protein S19 (AA 1 - 133) [Mesocricetus auratus] >gi 57858 ribosomal protein S24 [Rattus norvegicus] >gi 57722 ribosomal protein S24 (AA 1-133) [Rattus	gi 337506	96	503	87	87	HSA YG46	Lung, Pancreas, Breast/Ovarian
37	670729	acidic ribosomal phosphoprotein (P1) [Homo sapiens] >pir B27125 R6HUP1 acidic ribosomal protein P1 - human Length = 114	gi 190234	74	496	100	100	H2CBM17	Lung, Pancreas, Colon, Breast/Ovarian
38	674123	collagen type VI, alpha 3 chain [Homo sapiens] >sp E1292418 E1292418 COLLAGEN TYPE VI, ALPHA 3 CHAIN. Length = 3176	gn P1D1e1292418	40	438			11YACJ55	Lung, Pancreas
39	676496		gn P1D1e1292418	250	1029	98	98	HSLIC82	Lung, Pancreas
40	678162	TAXREB107 [Homo sapiens] >pir S1803 S1803 TAXREB107 - human Length = 288	gn P1D1d1005017	528	974	100	100	HBJJA02	Lung, Pancreas, Breast/Ovarian

41	678248	dolichol-phosphate-mannose synthase [Homo sapiens] >sp O60762 O60762 DOLICHOL-PHOSPHATE-MANNOSE SYNTHASE. >gnl PID d1026578 dolichol-phosphate-mannose synthase [Homo sapiens] {SUB 1-120; Length = 260}	gnl PID d1026577	3	770	100	100	HMTAK71	Lung, Pancreas
42	683668	alpha 1 (I) chain propeptide [Homo sapiens] >gi 180380 alpha-1 type I collagen [Homo sapiens] {SUB 64-201; Length = 1040}	gi 180392	566	1912	94	94	HWHGV07	Lung, Pancreas, Breast/Ovarian
43	693172	Q1Z 7F5 [Homo sapiens] >gi 189266 may code for Wilms' tumor-related protein [Homo sapiens] >gi 190814 Wilms' tumor-related protein [Homo sapiens] >gi 1203971 QM gene product [Homo sapiens] >bbs 135740 QM [human, nonneurogenic Wilms' microcell hybrid c	gi 184407	23	214	97	100	HNHW05	Lung, Pancreas, Breast/Ovarian
44	694303			2824	3219			HOGAV47	Lung, Breast/Ovarian
45	695042	Description: KRAB zinc finger protein; this is a splicing variant that contains a stop codon and frame shift between the KRAB box and the zinc finger region; Method: conceptual translation supplied by author [Homo sapiens] >sp Q13359 Q13359 KRAB ZINC FING	gi 1049295	471	680	74	91	HNHXX26	Pancreas, Breast/Ovarian
46	699799	lipocortin (AA 1-346) [Homo sapiens] >pir A03080 LUHU annexin I - human >sp P04083 ANX1_HUMAN ANNEXIN I (LIPOCORTIN I) (CALPACTIN II) (CHROMOBINDIN 9) (P35) (PHOSPHOLIPASE A2 INHIBITORY PROTEIN). {SUB 2-346; Length = 346}	gi 34388	3	1121	100	100	HNDAAS1	Lung, Breast/Ovarian

47	702216	dihydrodiol dehydrogenase [Homo sapiens] >gi 487135 hepatic dihydrodiol dehydrogenase [Homo sapiens] >gi 181549 dihydrodiol dehydrogenase [Homo sapiens] >pir A53436 A53436.3-alpha- hydroxysteroid/dihydrodiol dehydrogenase (EC 1.1.1.-) - human >sp Q04828 DB	gi 452484	41	1048	95	95	HNALC11	Lung, Pancreas
48	703015	latent transforming growth factor-beta-binding protein - human Length = 1820	pir A55494 A55494	3	587	100	100	HTCOX28	Lung, Pancreas
49	706391	vacuolar H+ ATPase proton channel subunit [Homo sapiens] >pir A39367 A39367 H+-transporting ATPase (EC 3.6.1.35) chain PKD1 - human Length = 155	gi 189676	29	622	85	85	HMA1BL73	Lung, Breast/Ovarian
50	706892	copper transport protein HAH1 [Homo sapiens] >sp O00244 O00244 COPPER TRANSPORT PROTEIN HAH1. Length = 68	gi 1945365	3	287	82	82	HUPDS83	Lung, Breast/Ovarian
51	706924			2847	3215			HRAEB20	Lung, Breast/Ovarian
52	707642	ribosomal protein L8 [Homo sapiens] >gi 57704 ribosomal protein L8 [Rattus rattus] >gi 527178 ribosomal protein L8 [Mus musculus] >pir J0177 RSR TL8 ribosomal protein L8, cytosolic - rat >pir N0923 N0923 ribosomal protein L8, cytosolic - human >gi 3851	gi 433899	1	516	94	94	HSLR0344	Lung, Pancreas, Colon, Breast/Ovarian
53	710369			99	611			HSPA181	Lung, Pancreas, Breast/Ovarian
54	718826			581	877			HSLFK68	Lung, Breast/Ovarian

55	719790	lipocortin II [Homo sapiens] >pirIA23942 LUHU36 annexin II - human >sp P07355 ANX2_HUMAN ANNEXIN II (LIPOCORTIN II) (CALPACTIN I HEAVY CHAIN) (CHROMOBINDIN 8) (P36) (PROTEIN I) (PLACENTAL ANTICOAGULANT PROTEIN IV) (PAP-IV). (SUB 2-339) >sp G545387 G545387	gnl PID d1000439	3	869	98	98	HKABK62	Lung, Pancreas
56	720222	homology with 16.7 KD putative viral protein YUBI_NpVAC [Caenorhabditis elegans] Length = 250	gnl PID c1346018	34	729	45	60	HSKEP04	Lung, Pancreas, Breast/Ovarian
57	724033			1	654			HPIBV92	Lung, Pancreas, Breast/Ovarian
58	724767	epsilon isoform of 61kDa regulatory subunit of PP2A [Homo sapiens] >gi 1478070 protein phosphatase B56-epsilon [Homo sapiens] >sp Q16537 Q16537_EPSILON_ISOFORM_OF 61KDA_REGULATORY_SUBUNIT_OF_PP2A. >gi 1022892 protein phosphatase PP2A0 B' subunit delta is	gnl PID e220196	71	526	100	100	HKABI59	Lung, Breast/Ovarian
59	727065	ATPase [Homo sapiens] Length = 617	gi 291868	228	1010	99	99	HELGY15	Lung, Pancreas
60	727246	(AB009282) cytochrome b5 [Homo sapiens] >sp O43169 O43169_CYTOCHROME_B5 (FRAGMENT), Length = 146	gnl PID d1024640	3	509	96	98	HCFMH52	Lung, Colon
61	727932			41	199			HLJDO53	Lung, Breast/Ovarian
62	731167	Sec23 protein [Homo sapiens] Length = 765	gnl PID e236013	1	987	99	99	HDTEM51	Lung, Pancreas

63	732514	lysophosphatidic acid acyltransferase-alpha [Homo sapiens] >gil2253613 putative lysophospholipid acyltransferase [Homo sapiens] >gnlPDIc28645 1-acylglycerol-3-phosphate O-acyltransferase [Homo sapiens] >spQ99943 PLCA_HUMAN 1-ACYL-SN-GLYCEROL-3-PHOSPHA	gil2155238	3	794	99	99	HLDBX26	Pancreas, Prostate
64	734080			1	567			HFIBK44	Lung, Breast/Ovarian
65	734288	cysteinyI-RNA synthetase [Homo sapiens] Length = 595	gil927229	154	2067	99	99	HKABU01	Lung, Pancreas
66	739448	Nascent polypeptide associated complex alpha subunit [Homo sapiens] >gil4092060 (AF034187) alpha NAC [Homo sapiens] >pirS49326 S49326 Nascent polypeptide associated complex alpha chain - human >spQ13765 Q13765 NASCENT POLYPEPTIDE ASSOCIATED COMPLEX ALPH	gil556642	441	1184	82	82	HKGA131	Lung, Breast/Ovarian
67	739668			2	484			HAPTL07	Lung, Pancreas
68	740060	Diff33 gene product [Homo sapiens] >spQ13530 Q13530 PLACENTAL PROTEIN DIFF33. Length = 494	gil293563	76	1536	94	94	HMEGB82	Lung, Pancreas
69	741560			3	296			HCGM112	Lung, Colon
70	742543	human gamma-glutamyl hydrolase [Homo sapiens] >spQ92820 Q92820 HUMAN GAMMA-GLUTAMYL HYDROLASE (EC 3.4.22.12). Length = 318	gil2951931	187	804	99	100	HE2BG62	Lung, Colon, Breast/Ovarian
71	742831			25	297			HCDAL47	Pancreas, Colon

72	745327	channel-like integral membrane protein [Homo sapiens] >gil1314304 channel-like integral membrane protein [Homo sapiens] >pir A41616 A41616 erythrocyte integral membrane protein 28K - human >sp p29972 AQP1_HUMAN AQP1/ANION CHANNEL PROTEIN FOR RE	gil180501	1	534	98	98	HWHPM73	Lung, Pancreas
73	745695	Mac-2 binding protein [Homo sapiens] >gil483474 90K gene product [Homo sapiens] >pir A47161 A47161 Mac-2-binding glycoprotein precursor - human >sp Q08380 Q08380 MAC-2 BINDING PROTEIN PRECURSOR. Length = 585	gil307153	886	2016	98	98	HOBBN02	Lung, Pancreas
74	750316	(AF029890) hepatitis B virus X interacting protein [Homo sapiens] >sp O43504 O43504 HEPATITIS B VIRUS X INTERACTING PROTEIN. Length = 91	gil2745883	99	398	100	100	HKMLD65	Lung, Pancreas, Breast/Ovarian
75	750522			172	906			HUKF158	Lung, Pancreas, Colon, Breast/Ovarian
76	750583			58	189			HBHJB66	Lung, Breast/Ovarian
77	751020			1	480			HEBAE80	Lung, Breast/Ovarian
78	752196			1	120			HL1A167	Pancreas, Prostate
79	753084	UGTrel1 [Homo sapiens] >pir C5024 C5024 UDP-galactose transporter related isozyme 1 - human >sp P78383 P78383 UGTREL1. Length = 322	gil1669560	53	1168	87	87	HDPKG74	Lung, Pancreas
80	754957	The ha1237 gene product is related to S.pombe rad21 gene product. [Homo sapiens] Length = 631	gilPID d1008135	242	1330	94	94	HWBCB01	Lung, Pancreas

81	756557	myosin I heavy chain [Rattus norvegicus] >pir A45439 A45439 myosin I heavy chain - rat >sp Q05096 Q05096 MYOSIN HEAVY CHAIN I. Length = 1136	gil56733	1	888	94	94	HE8AF67	Lung, Pancreas, Colon, Breast/Ovarian
82	756712	5-lipoxygenase activating protein [Homo sapiens] >pir A39824 A39824 5-lipoxygenase-activating protein - human >sp P20292 FLAP_HUMAN 5- LIPXYGENASE ACTIVATING PROTEIN (FLAP) (MK-886-BINDING PROTEIN). Length = 161	gil182658	1457	1729	99	100	IISYBW76 HCABA08	Lung, Pancreas Lung, Colon
83	757414			1	477				
84	757614	tetrapeptide repeat protein [Homo sapiens] >sp Q99614 Q99614 TETRAPETRICPEPTIDE REPEAT PROTEIN. Length = 292	gil1688074	83	991	100	100	HME/SL3	Lung, Pancreas, Breast/Ovarian
85	757815	(AF038604) contains similarity to Drosophila ovarian tumor locus protein (GB:X13693) [Caenorhabditis elegans] >sp O44438 O44438 B0546.2 PROTEIN. Length = 346	gil2702370	2	988	58	81	HCHOL74	Lung, Breast/Ovarian
86	759878	nuclear pore complex protein NUP107 [Rattus norvegicus] >pir A54142 A54142 nucleoporin NUP107 - rat >sp P52590 N107_RAT NUCLEAR PORE COMPLEX PROTEIN NUP107 (NUCLEOPORIN NUP107) (107 KD NUCLEOPORIN) (P105). Length = 926	gil510717	526	1833	86	88	HINTAP78	Lung, Breast/Ovarian
87	760227	(AC003040) putative nicotinic phosphoribosyltransferase [Arabidopsis thaliana] >sp O80459 O80459 PUTATIVE NICOTINATE PHOSPHORIBOSYLTRANSFERASE. Length = 574	gil3242705	2	484	52	71	HCHMM71	Pancreas, Breast/Ovarian

88	760312	chondroitin sulfate proteoglycan versican V0 splice-variant precursor peptide [Homo sapiens] >sp P1361 PGCV_HUMAN VERSICAN CORE PROTEIN PRECURSOR (LARGE FIBROBLAST PROTEOGLYCAN) (CHONDROITIN SULFATE PROTEOGLYCAN CORE PROTEIN 2) (GLIAL HYALURONATE-BINDIN	gij608515	993	3215	99	99	IIMVDD07	Lung, Pancreas
89	766051			1	627			HMAFA79	Lung, Breast/Ovarian
90	767593			327	497			HCECT76	Pancreas, Colon
91	768053	(AF039688) antigen NY-CO-3 [Homo sapiens] >sp O60525 O60525 ANTIGEN NY-CO-3 (FRAGMENT). Length = 192	gij3170176	251	625	99	99	HTPE171	Pancreas, Breast/Ovarian
92	768055	ATP synthase gamma-subunit [Homo sapiens] >gnl P1D d1004512 ATP synthase gamma-subunit [Homo sapiens] >pir A49108 A49108 H+-transporting ATP synthase (EC 3.6.1.34) gamma chain - human >sp P36542 ATPG_HUMAN ATP SYNTHASE GAMMA CHAIN, MITOCHONDRIAL PRECURSOR	gnl P1D d1004511	32	949	100	100	HAAJQ70	Lung, Pancreas
93	769685	src-like tyrosine kinase (put.), putative [Homo sapiens] Length = 537	gij338228	1005	1409	100	100	HRADN48	Lung, Pancreas, Colon, Breast/Ovarian
94	771920	F36D4.2 gene product [Caenorhabditis elegans] >sp Q20100 Q20100 COSMID F36D4. Length = 224	gij1245686	711	1562	58	77	HAIDT44	Lung, Pancreas
95	772790	cell division inhibitor [Synecocystis sp.] >pir S77404 S77404 cell division inhibitor - Synecocystis sp. (PCC 6803) >sp P73467 P73467 CELL DIVISION INHIBITOR. Length = 339	gnl P1D d1018240	145	1158	35	54	HCEOT95	Lung, Breast/Ovarian



96	772916	similar human ZFY protein. [Homo sapiens] >sp Q92610 Q92610 MYELOBLAST KIA0211. Length = 1267	gn P D d 01389	3	965	99	99	HCF1126	Lung, Pancreas
97	773225								
98	773632	lrs [Homo sapiens] >gi 2731383 HCF receptor substrate Hrs [Homo sapiens] >sp O14964 O14964 HRS, COMPLETE CDS. Length = 777	gn P D d 024245	52 1	504 309	98	98	HCLB178 HCFVQ60	Lung, Pancreas Pancreas, Prostate, Breast/Ovarian
99	774364	(AF080561) SYT interacting protein SIP [Homo sapiens] >sp O75932 O75932 SYT INTERACTING PROTEIN SIP. Length = 669	gi 3746787	1	408	100	100	HCHAR77	Pancreas, Breast/Ovarian
100	775355								
101	775844	rft transforming protein [Homo sapiens] >pir A28101 TVHURF ret finger protein - human >gn P D c308255 RFP [Homo sapiens] {SUB 250- 513} Length = 513	gi 337372	1599 138	1781 1877	92	92	HDTBY31 HISCU10	Lung, Pancreas Lung, Pancreas
102	777760	(AF015040) NUMB protein [Homo sapiens] >sp G4102705 G4102705 NUMB PROTEIN. >gi 4050088 (AF109907) S171 [Homo sapiens] {SUB 79-603} >gi 887362 (IKF): putative [Homo sapiens] {SUB 469-603} Length = 603	gi 4102705	62	1372	88	88	HMSHK67	Pancreas, Breast/Ovarian
103	779837	tazarotene-induced gene 2 [Homo sapiens] >sp Q9969 Q9969 TAZAROTENE-INDUCED GENE 2. Length = 163	gi 1848264	88	567	97	98	HSWBV38	Lung, Pancreas
104	780769	(AF084259) bromodomain-containing protein BP75 [Mus musculus] >sp O88665 O88665 BROMODOMAIN-CONTAINING PROTEIN BP75. Length = 651	gi 3493162	100	762	35	58	HUJBS08	Lung, Pancreas
105	781445			496	1443			HMVAP52	Pancreas, Breast/Ovarian

106	781531	lumican [Homo sapiens] Length = 338	gi 699577	1	486	100	100	HCHAF71	Pancreas, Breast/Ovarian
107	783018	ovary2 [Drosophila melanogaster] >sp Q27924 Q27924 OVARY2. >gi 1208729 ovary2 [Drosophila melanogaster] {SUB 386-515} Length = 545	gi 1208732	120	674	58	76	HTPCZ45	Pancreas, Breast/Ovarian
108	783097	myogenic repressor 1-m1 [Homo sapiens] >sp Q99750 Q99750 MYOGENIC REPRESSOR 1- MF. Length = 246	gi 1763615	413	919	85	85	HMWGR19	Lung, Colon
109	784198	(AJ005893) JM26 [Homo sapiens] >sp Q60828 Q60828 JM26 PROTEIN, COMPLETE CDS (CLONE LLOXNC01U138D3 (BAYLOR COLLEGE)). Length = 265	gn P P D c 289747	80	943	81	81	HINTNB85	Lung, Pancreas, Breast/Ovarian
110	784868	WW-domain binding protein 1 [Mus musculus] >sp P97764 P97764 WW-DOMAIN BINDING PROTEIN 1. Length = 305	gi 1777577	1	969	77	85	HINTNQ08	Lung, Pancreas, Breast/Ovarian
111	785428	translation initiation factor 5 [Homo sapiens] >sp P55010 P55010 HUMAN EUKARYOTIC TRANSLATION INITIATION FACTOR 5 (EIF- 5). Length = 431	gi 1229140	308	1606	87	87	IIPMC114	Lung, Pancreas, Breast/Ovarian
112	785845			67	1350			HCGBE06	Lung, Colon, Breast/Ovarian
113	785854			3	509			HUSXJ65	Lung, Pancreas
114	786705			64	180			HBJJB89	Lung, Pancreas, Breast/Ovarian
115	787186			319	975			HUKBB89	Lung, Pancreas
116	787279	proteasome subunit z [Homo sapiens] >sp Q99436 Q99436 PROTEASOME SUBUNIT Z. Length = 277	gn P P D c 1007816	80	856	94	94	HKAJZ91	Lung, Breast/Ovarian
117	789002			178	402			HATBM56	Lung, Pancreas, Breast/Ovarian

118	789008	1.8 kb mRNA (AA 1-84) [Homo sapiens] >pir S03384 S03384 hypothetical protein (IGF-II 3' region) - human >sp P09565 IG2R_HUMAN PUTATIVE INSULIN-LIKE GROWTH FACTOR II ASSOCIATED PROTEIN. Length = 84	gi 33000	1354	1737	100	100	HISCN20	Lung, Pancreas
119	789555	(AL035247) hypothetical trp-asp repeat protein [Schizosaccharomyces pombe] Length = 760	gn PID e1371207	124	1815	42	66	HTTCB23	Pancreas, Breast/Ovarian
120	789631			192	320			HLICN93	Lung, Pancreas, Colon
121	789779			1	396			HCHMS40	Colon, Breast/Ovarian
122	790387			3	527			HLMNA32	Colon, Breast/Ovarian
123	790461	(AF084445) phospholipid scramblase [Homo sapiens] >gn PID d1033532 (AB006746) hMimTRA1b [Homo sapiens] >gi 4092081 (AF098642) phospholipid scramblase; plasma membrane phospholipid scramblase [Homo sapiens] >sp O15162 O15162 PHOSPHOLIPID SCRAMBLASE. >sp G4	gi 2282601	105	1193	99	99	HTGAV10	Lung, Pancreas, Breast/Ovarian
124	790931			2	394			HBCAO30	Pancreas, Breast/Ovarian
125	791176	(AB002107) hPer [Homo sapiens] >gi 2435507 (AF022991) Rigui [Homo sapiens] >sp O15534 O15534 RIGUI. Length = 1290	dbj AB002107_1	3	1034	90	90	IINFJC67	Lung, Pancreas
126	791983			637	837			HBJLJE45	Lung, Pancreas, Colon, Breast/Ovarian

127	792339	(AF020833) eukaryotic translation initiation factor 3 subunit [Homo sapiens] >sp O14801 O14801 EUKARYOTIC TRANSLATION INITIATION FACTOR 3 SUBUNIT. Length = 320	gi 2460200	94	1068	94	94	HDPPX89	Lung, Pancreas, Breast/Ovarian
128	792749	protein arginine N-methyltransferase [Rattus norvegicus] >sp Q63009 ANM1_RAT PROTEIN ARGININE N-METHYLTRANSFERASE 1 (EC 2.1.1.-). Length = 353	gi 1390025	34	1104	95	96	HDQEP64	Lung, Breast/Ovarian
129	792961	(AF036249) polymerase I-transcript release factor; PTRF [Mus musculus] >sp O54724 O54724 POLYMERASE I AND TRANSCRIPT RELEASE FACTOR (POLYMERASE I-TRANSCRIPT RELEASE FACTOR). Length = 392	gi 2674195	778	1305	85	86	HMEKG25	Lung, Breast/Ovarian
130	793206	dJ1409.2 (Melanoma-Associated Antigen MAGE LIKE) [Homo sapiens] >sp O76058 O76058 dJ1409.2 (MELANOMA-ASSOCIATED ANTIGEN MAGE LIKE). Length = 606	gn P1D1e1311294	889	1365	99	99	111WFN71	Lung, Pancreas
131	793249	proliferation associated gene (pag) gene product [Homo sapiens] >pir A46711 A46711 proliferation associated gene (pag) protein - human Length = 199	gi 287641	3	701	100	100	HJAAE81	Lung, Pancreas, Breast/Ovarian
132	793626	alpha mannosidase II isozyme [Homo sapiens] >sp P49641 MA2X_HUMAN ALPHA-MANNOSIDASE IIX (EC 3.2.1.114) (MANNOSYL-OLIGOSACCHARIDIE 1,3-1,6-ALPHA-MANNOSIDASE) (MAN IIX). Length = 1139	gn P1D1d1010153	119	640	99	99	HWABS13	Lung, Pancreas

133	794417	(A1047470) malate dehydrogenase precursor [Homo sapiens] >sp O43682 O43682 MALATE DEHYDROGENASE (EC 1.1.1.37) PRECURSOR (EC 1.1.1.37). Length = 338	gil2906146	3	1142	99	99	HPH003	Lung, Pancreas, Breast/Ovarian
134	795197			82	888			HDPF126	Lung, Breast/Ovarian
135	795251	GAP SH3 binding protein [Homo sapiens] >sp Q13283 Q13283 GAP SH3 BINDING PROTEIN. Length = 466	gil1051170	101	1531	91	91	HE8FJ92	Pancreas, Breast/Ovarian
136	795752			2	1018			HWBDR92	Lung, Pancreas
137	796261	ubiquitin carrier protein E2 - human >gil181916 ubiquitin carrier protein [Homo sapiens] (SUB 23- 247) Length = 247	pir B42856 B42856	3	851	87	87	HCHHQ06	Colon, Breast/Ovarian
138	796933	lumican [Homo sapiens] Length = 338	gil699577	49	1107	94	94	HPMSD56	Lung, Pancreas, Prostate, Colon, Breast/Ovarian
139	799424			525	1553			HEONK47	Lung, Pancreas, Breast/Ovarian
140	799698			1	426			HCHAM08	Colon, Breast/Ovarian
141	800351	DNAJ homolog [Homo sapiens] >gil127833 heat shock protein hsp40 homolog [Homo sapiens] >pir G02272 G02272 heat shock protein hsp40 homolog - human >sp Q1343 Q13431 HEAT SHOCK PROTEIN HSP40 HOMOLOG. Length = 178	gil1518918	282	860	83	84	HEMFP05	Pancreas, Breast/Ovarian

142	800573	26S protease subunit [Sus scrofa] >gil3193258 (AF069053) proteasome subunit SUG1 [Bos taurus] >gnl PI d 012606 proteasomal ATPase (rat SUG1) [Rattus norvegicus] >gnl PI d 023806 (AB000491) proteasome p45/SUG [Rattus norvegicus] >gnl PI d 019326 mSUG1 pr	gnl PI d c235521	178	1383	93	93	HCEVS28	Lung, Breast/Ovarian
143	805815			15	1055			HCI1AP80	Lung, Colon, Breast/Ovarian
144	806445			711	1028			HTELC67	Lung, Pancreas
145	810309	(AF098482) transcriptional coactivator p52 [Homo sapiens] >sp G4050034 G4050034 TRANSCRIPTIONAL COACTIVATOR P52. Length = 333	gi 4050034	226	741	61	75	HNTDX22	Lung, Pancreas
146	811022			168	881			HISEA13	Lung, Pancreas
147	811023			13	234			HLWAW17	Lung, Pancreas, Colon, Breast/Ovarian
148	811143	cytokine inducible SH2-containing protein [Mus musculus] >pir S55551 S55551 cytokine-inducible protein CIS - mouse >sp Q62225 Q62225 CYTOKINE INDUCIBLE SH2-CONTAINING PROTEIN (SH2 DOMAIN CONTAINING PROTEIN INDUCED BY MULTIPLE CYTOKINES, SIC). Length = 257	gnl PI d 01007285	3	887	90	92	IIIQ1VA25	Lung, Breast/Ovarian
149	811381	FIN14 gene product [Mus musculus] >sp Q61077 F114_MOUSE FIBROBLAST GROWTH FACTOR INDUCIBLE PROTEIN 14 (FIN14). Length = 61	gi 1353711	1338	1511	86	91	HLYEK93	Colon, Breast/Ovarian

150	811595	CIRP [Homo sapiens] >gi 2924760 (AC004258) CIRP [Homo sapiens] >gi 2541973 (AF021336) DNA damage-inducible RNA binding protein [Homo sapiens] >sp Q1401 Q1401 GLYCINE- RICH RNA BINDING PROTEIN CIRP. Length = 172	gnl PID d1011874	1	609	100	100	HDTLA92	Pancreas, Breast/Ovarian
151	813000	Tera [Mus musculus] >sp P70361 P70361 TERA. Length = 277	gi 1575505	95	850	84	86	HDPVZ64	Pancreas, Breast/Ovarian
152	813288	tau gene product [Homo sapiens] >gi 31305 tau 1 gene product [Homo sapiens] >pir JC1278 JC1278 ubiquitin-like protein / ribosomal protein S30, cytosolic - human Length = 133	gi 31303	1	510	86	86	HCIMQ63	Lung, Breast/Ovarian
153	813431	DAP-1 [Homo sapiens] >pir 37274 37274 death- associated protein 1 - human >sp P51397 DAP1_HUMAN DEATH- ASSOCIATED PROTEIN 1 (DAP-1). Length = 102	gi 434845	3	470	89	89	HWHSQ570	Lung, Pancreas
154	813450	PISSLRE gene product [Homo sapiens] >pir S49330 S49330 serine/threonine kinase (EC 2.7.1.-) pissre - human >pir 38116 38116 gene PISSLRE protein - human >sp Q15131 Q15131 PISSLRE MRNA. Length = 360	gi 556651	1	651	100	100	HCECJ73	Lung, Pancreas
155	813478	retinoblastoma-binding protein mRbAp48 [Mus musculus] >pir 49366 49366 retinoblastoma- binding protein mRbAp48 - mouse Length = 461	gi 1016275	1	1398	99	100	HABH20	Lung, Pancreas, Breast/Ovarian
156	813505	ribosomal protein L23a [Homo sapiens] >gi 306549 homology to rat ribosomal protein L23 [Homo sapiens] {SUB 10-156} Length = 156	gi 404015	2	496	100	100	IDAHR53	Lung, Pancreas

157	815552	(AJ011497) Claudin-9 [Homo sapiens] >sp E1363658 E1363658 CLAUDIN-9. Length = 211	gnl PID e1363658	317	808	95	96	HUFEH29	Lung, Colon
158	815606	Ki-1/57 intracellular antigen [Homo sapiens] >sp O75804 O75804 Ki-1/57 INTRACELLULAR ANTIGEN (FRAGMENT). Length = 299	gi 3403154	218	1303	90	95	HDPRY63	Lung, Pancreas, Breast/Ovarian
159	816048	neutral protease alpha subunit [Homo sapiens] >gi 35328 protease small subunit (aa 1-268) [Homo sapiens] >gi 1905903 (AD001527) calcium-dependent protease, small (regulatory) subunit (calpain) (calcium-activated neutral proteinase) (CANP) [Homo sapiens] >	gi 179909	24	644	95	96	HTLCZ60	Lung, Breast/Ovarian
160	822978	(AF003130) similar to Achlya ambisexualis antheridiol steroid receptor (NID:g166306) [Caenorhabditis elegans] >sp O01757 O01757 SIMILAR TO ACHLYA AMBISEXUALIS ANTHERIDIOL STEROID RECEPTOR. Length = 1043	gi 2088668	94 1449 992	156 1775 2617	60	78	HODEN46	Lung, Pancreas
161	823616							HCHEM179	Pancreas, Colon
162	823981							HWHQH79	Lung, Breast/Ovarian
163	824364	drebrin E2 [Homo sapiens] >gnl PID d1005005 drebrin E [Homo sapiens] >pir JN0809 JN0809 drebrin E (clone gDbh13) - human >sp Q16643 DREB_HUMAN DREBRIN E. Length = 649	gi 392890	1	606	84	84	HCHPR34	Colon, Breast/Ovarian



164	824423	UDP-GalNAc:polypeptide N-acetylgalactosaminyl transferase [Homo sapiens] >pir JC4223 JC4223 polypeptide N-acetylgalactosaminyltransferase (EC 2.4.1.41) - human >sp Q10472 PAGT_HUMAN POLYPEPTIDE N-ACETYL GALACTOSAMINYLTRANSFERASE (EC 2.4.1.41) (PROTEIN- UDP	gj 071459	61	1743	100	100	HPWD1L83	Lung, Pancreas
165	825279			36	602			HEEDN61	Lung, Pancreas
166	825442			1	900			HTODA45	Colon, Breast/Ovarian
167	825548	ancient ubiquitous 46 kDa protein AUP46 precursor [Mus musculus] >sp P70295 P70295 ANCIEN <sup>T</sup> UBIQUITOUS PROTEIN PRECURSOR (AUP1), Length = 416	gj 1517822	473	1504	81	84	HLUDB77	Lung, Breast/Ovarian
168	825725	hNop56 [Homo sapiens] >sp Q00367 NOP56_HUMAN NUCLEAR PROTEIN NOP56, Length = 602	gn P1D1e1188703	25	723	99	99	HMW1V57	Lung, Pancreas
169	826639	H.sapiens mRNA for rat translocon-associated protein delta homolog [Homo sapiens] >gn P1D1e212192 translocon-associated protein delta subunit precursor [Homo sapiens] >gn P1D1e220312 translocon-associated protein delta subunit precursor [Homo sapiens] >	gj 1071681	1	561	100	100	HPVX93	Lung, Colon, Breast/Ovarian
170	827079	(AL009171) 62D9.a [Drosophila melanogaster] >sp E1198294 E1198294 62D9.A, Length = 1305	gn P1D1e1198294	53	2176	71	85	HDAAD02	Lung, Breast/Ovarian

171	827153	pancreatitis-associated protein [Homo sapiens] >gi312807 preproinsulin [Homo sapiens] >bb5121222 PAP-H=pancreatitis-associated protein [human, pancreas, Peptide, 175 aa] [Homo sapiens] >gi P1D1003233 PAP homologous protein [Homo sapiens] >pirA49616/A49	gi482909	54	602	90	90	HLQBS95	Pancreas, Colon, Breast/Ovarian
172	827351			1	639			HSKJE35	Colon, Breast/Ovarian
173	827503	(AC004003) serine/threonine kinase RICK; match to protein AF027706 (PID:g3123887) and mRNA AF027706 (NID:g3123886) [Homo sapiens] >gi3290172 (AF064824) CARD-containing ICE associated kinase [Homo sapiens] >gi3342910 (AF078530) receptor interacting prote	gi3264574	255	1886	98	98	HLAAB36	Lung, Breast/Ovarian
174	827563	rhophilin [Mus musculus] >spQ61085/Q61085 GTP-RHO BINDING PROTEIN 1 (RHOPILIN); Length = 643	gi1176422	6	776	81	91	IIBGDH11	Colon, Breast/Ovarian
175	827565	serine protease [Homo sapiens] Length = 492	gi2507613	1	744	55	68	HCHAK72	Lung, Pancreas, Colon, Breast/Ovarian
176	827893	homology with GTP binding protein; putative [Caenorhabditis elegans] >pirS44605/S44605 C02F5.3 protein - Caenorhabditis elegans Length = 573	gi289610	165	836	62	75	HMSD138	Lung, Pancreas
177	828072			1147	1305			HTECA53	Lung, Pancreas, Breast/Ovarian
178	828228			1105	1314			HWLA1178	Prostate, Colon

179	828241	cathepsin O [Homo sapiens] >pir A55090 A55090 cathepsin O (EC 3.4.-.-) precursor - human >sp P43234 CATO_HUMAN CATHEPSIN O PRECURSOR (EC 3.4.22.-). Length = 321	gil574804	2	1012	93	93	HWBBDP30	Lung, Pancreas, Prostate
180	828287	histone (H2A.Z) [Bos taurus] >gil410 histone H2A.Z (AA 1-127) [Bos taurus] >gil184060 histone (H2A.Z) [Homo sapiens] >gil31975 histone H2A.Z (AA 1-127) [Homo sapiens] >gil3649600 histone [Homo sapiens] >gil204599 histone (H2A.Z) [Rattus norvegicus] >gil57	gil163150	171	572	100	100	HUSIS02	Lung, Pancreas, Prostate, Breast/Ovarian
181	828364			663	1340			HWIHC117	Pancreas, Breast/Ovarian
182	828371	complement component C1s [Homo sapiens] >gil179648 complement subcomponent C1s precursor [Homo sapiens] >gil763110 complement protein C1s precursor [Homo sapiens] >pir A40496 C1HUS complement subcomponent C1s (EC 3.4.21.42) precursor - human >sp P09871 C1	gil179646	4	2283	97	97	HLQCQ12	Lung, Pancreas, Colon, Breast/Ovarian
183	828403	DNA-binding protein [Homo sapiens] >pir A44478 A44478 probable cell growth or differentiation regulator (alternatively spliced type 1 transcript) - human >sp Q02833 Q02833 PUTATIVE TRANSCRIPTIONAL REGULATORY PROTEIN HRC1. Length = 373	gil184390	1	648	98	98	HDTHL82	Lung, Pancreas, Colon
184	828501	(AF056302) eIF-2alpha kinase [Drosophila melanogaster] >sp O61651 O61651 EIF-2ALPHA KINASE. Length = 1589	gil3046551	1	1812	36	58	HHMDC73	Lung, Colon, Breast/Ovarian

185	828520	(A1010840) ATP-dependent RNA helicase [Homo sapiens] >sp E1321519 E1321519 ATP-DEPENDENT RNA HELICASE (FRAGMENT). Length = 420	gnl P1D e1321519	445	1821	91	91	HRGBN47	Prostate, Breast/Ovarian
186	828527			723	926			HSKGG05	Lung, Pancreas, Prostate, Breast/Ovarian
187	828538			332	976			HPWDF55	Lung, Prostate, Breast/Ovarian
188	828541	pre-pump-1 proteinase (AA -17 to 250) [Homo sapiens] >gi35803 PUMP [Homo sapiens] >pir B28816 KCHUM matrixysin (EC 3.4.24.23) precursor - human >sp P09237 COG7_HUMAN MATRIXIN PRECURSOR (EC 3.4.24.23) (PUMP-1 PROTEASE) (UTERINE METALLOPROTEINASE) (MATRI	gi35799	43	933	100	100	HRAC132	Pancreas, Prostate, Colon
189	828549	thrombospondin 2 [Homo sapiens] >pir A47379 TSHUP2 thrombospondin 2 precursor - human Length = 1172	gi307506	26	1738	94	94	HFIAL22	Pancreas, Colon
190	828562			1	342			HPWBR24	Pancreas, Prostate
191	828576			3	731			HPTVU91	Pancreas, Prostate, Colon
192	828602			1050	1568			HPRAT58	Lung, Prostate
193	828628	tumor-associated antigen [Homo sapiens] >pir A36056 A36056 tumor-associated antigen CO-029 - human >sp P19075 CO02_HUMAN TUMOR-ASSOCIATED ANTIGEN CO-029. Length = 237	gi180926	307	1029	94	94	HPRCM33	Pancreas, Prostate, Colon

194	828667	cytochrome c-1 [Homo sapiens] >sp P08574 CY1_HUMAN CYTOCHROME C1, HEME PROTEIN PRECURSOR. >gi 181238 cytochrome c1 [Homo sapiens] {SUB 99-325}; Length = 325	gi 181240	2	1006	85	85	HKAOB02	Pancreas, Breast/Ovarian
195	828684	p55CDC [Homo sapiens] >pir A5602 A56021 probable cell division control protein p55CDC - human >sp Q12834 Q12834 P55CDC; Length = 499	gi 468032	41	1573	92	92	IIPAE35	Pancreas, Prostate
196	828727	(AF044954) NADH:ubiquinone oxidoreductase PDSW subunit [Homo sapiens] >gi 416509  (AF088991) NADH:ubiquinone oxidoreductase PDSW subunit [Homo sapiens] Length = 172	gi 416442	3	629	93	93	HMCBB12	Lung, Prostate, Breast/Ovarian
197	828734	homologue of Drosophila Fat protein [Homo sapiens] >sp Q14517 Q14517 CADHERIN- RELATED TUMOR SUPPRESSOR HOMOLOG PRECURSOR (FAT PROTEIN HOMOLOG). >gi P1D1022418 cadherin [Homo sapiens] {SUB 993-1132}; Length = 4590	gi 1107687	1	657	99	99	HSRAB84	Pancreas, Colon, Breast/Ovarian
198	828750	(AF035940) similar to mago nashi [Homo sapiens] >gi 2330011 (AF007862) mm-Mago [Mus musculus] >gi 2909828 (AF035939) similar to mago nashi [Mus musculus] >sp O35169 O35169 MM-MAGO. >sp G2909830 G2909830 MAGOH. >sp P50606 MGN_HUMAN MAGO NASHI PROTEIN HOMOL	gi 2909830	13	546	100	100	HPIAC11	Pancreas, Prostate, Breast/Ovarian

199	828842	(AB007191) AMY-1 [Homo sapiens] >gnl PID d1009980 c-myc binding protein [Homo sapiens] >sp Q99417 Q99417 C-MYC BINDING PROTEIN. Length = 103	gnl PID d1023271	1	363	98	100	HOUGA12	Pancreas, Prostate, Breast/Ovarian
200	828843	p48 [Homo sapiens] >sp P50502 HIP_HUMAN HSC70-INTERACTING PROTEIN (PROGESTERONE RECEPTOR-ASSOCIATED P48 PROTEIN). >gi 1857033 SCN6 gene product [Homo sapiens] {SUB 99-369} Length = 369	gi 904032	3	761	99	100	HOVBK85	Lung, Pancreas, Prostate
201	828851	(AF054284) spliceosomal protein SAP 155 [Homo sapiens] >sp G4033735 G4033735 SPliceosomal PROTEIN SAP 155. >gi 3387899 (AF070540) putative nuclear protein [Homo sapiens] {SUB 1011-1304} Length = 1304	gi 4033735	1	1029	98	98	HOSCA73	Pancreas, Prostate
202	828856	thymidine kinase (EC 2.7.1.21) [Homo sapiens] >gi 339719 thymidine kinase [Homo sapiens] >pir A27318 KHUT thymidine kinase (EC 2.7.1.21), cytosolic - human >sp P04183 KITH_HUMAN THYMIDINE KINASE, CYTOSOLIC (EC 2.7.1.21). >gi 339713 thymidine kinase [Homo sapiens]	gi 339709	1	804	99	100	HOHEN75	Prostate, Breast/Ovarian
203	828862	tyrosine kinase receptor [Homo sapiens] >pir B41527 B41527 transforming protein (axl(-)) - human Length = 885	gi 292870	1	417	98	98	HOHB190	Prostate, Breast/Ovarian
204	828870	TRAM protein [Homo sapiens] >pir S30034 S30034 translocating chain-associating membrane protein - human >sp Q15629 Q15629 TRAM PROTEIN. Length = 374	gi 37265	32	1279	94	94	HOEKU65	Lung, Pancreas, Colon

205	828873	precursor polypeptide (AA 31 to 1139) [Homo sapiens] >gi 538354 thrombospondin [Homo sapiens] {SUB 1-397} >gi 339669 thrombospondin [Homo sapiens] {SUB 1028-1170} >gi 532689 thrombospondin-1p180 [Homo sapiens] {SUB 364-422} Length = 1170	gi 37465	1	1398	100	100	100	H0HICJ26	Lung, Pancreas, Prostate, Colon, Breast/Ovarian
206	828892	keratin [Homo sapiens] >sp Q14533 Q14533 KERATIN (HAIR TYPE II BASIC KERATIN) (KERATIN LIKE). >gn P1D1e118093 hair type II basic keratin [Homo sapiens] {SUB 81-505} >gi 951272 keratin like [Homo sapiens] {SUB 249-505} >hhs 161491 type II hair keratin {cl	gn P1D1e321549	3	653	90	91	H0GAA83	Lung, Prostate, Breast/Ovarian	
207	828893	ESX [Homo sapiens] >gi 1841523 ESE-1b [Homo sapiens] >gi 2338756 (AF017307) Ets-related transcription factor [Homo sapiens] >gi 2384740 (AF016295) Ets transcription factor [Homo sapiens] >gi 2459797 epithelial-specific ets protein [Homo sapiens] >sp P78545	gi 1754538	36	1253	86	86	H0GAS09	Pancreas, Prostate, Colon, Breast/Ovarian	
208	828897	prolactin [Homo sapiens] >gi 862305 prolactin [Homo sapiens] >pir A57014 A57014 prolactin (EC 3.4.21.-) precursor - human >sp G365130 G365130 PROLACTIN=SERINE PROTEINASE (N-TERMINAL); {SUB 45-64} Length = 343	gi 1143194	59	811	92	92	H0CAY53	Pancreas, Colon, Breast/Ovarian	

209	828910	light chain 3 subunit of microtubule-associated proteins 1A and 1B [Rattus norvegicus] >pir A53624 A53624 microtubule-associated protein 1 light chain 3 - rat >sp Q62625 MP1.3_RAT MICROTUBULE-ASSOCIATED PROTEINS 1A/1B LIGHT CHAIN 3 (MAP1A/MAP1B LC3). {SUB	gj 455109	28	540	96	98	H01HDY41	Prostate, Colon
210	828927	cytochrome c oxidase subunit Va [Homo sapiens] >pir U0342 OTHU5A cytochrome-c oxidase (EC 1.9.3.1) chain Va precursor - human >sp P20674 COXA_HUMAN CYTOCHROME C OXIDASE POLYPEPTIDE VA PRECURSOR (EC 1.9.3.1). >gi 3859864 (AF067635) cytochrome c oxidase su	gi 695360	1	567	99	99	HHFJM88	Lung, Breast/Ovarian
211	828932	80K-H protein [Homo sapiens] >gi 1293640 protein kinase C substrate 80K-H [Homo sapiens] >pir A32469 A32469 80K protein H precursor - human >sp P14314 G19P_HUMAN PROTEIN KINASE C SUBSTRATE, 80 KD PROTEIN, HEAVY CHAIN (PKCSH) (80K-H PROTEIN). Length = 527	gi 182855	82	1026	83	83	HNTAC57	Lung, Pancreas, Prostate, Breast/Ovarian
212	828933	Csa-19 [Homo sapiens] Length = 217	gi 531171	439	852	97	98	HEMCA07	Lung, Pancreas, Breast/Ovarian
213	828941	ORF YJL115w [Saccharomyces cerevisiae] >gil171091 ASF1 [Saccharomyces cerevisiae] >pir S30766 S30766 ASF1 protein - yeast (Saccharomyces cerevisiae) >sp P32447 ASF1_YEAST ANTI-SILENCING PROTEIN 1. Length = 279	gi 1008304	1	729	59	74	HMCGRJ25	Lung, Pancreas, Colon, Breast/Ovarian



214	828957	F31C3.5 [Caenorhabditis elegans] >sp O62193 O62193 F31C3.5 PROTEIN. Length = 180	gn P1D1e1346411	3	635	37	68	HMWHG54	Prostate, Breast/Ovarian
215	828963	house-keeping protein [Mus musculus] >pir S27870 S27870 house-keeping protein - mouse >sp Q61669 Q61669 HOUSE-KEEPING PROTEIN 1. Length = 396	gi 193871	73	1293	55	77	HMWH1191	Lung, Prostate, Colon, Breast/Ovarian
216	828964			639	905			HMWFZ60	Pancreas, Prostate, Colon, Breast/Ovarian
217	828966	S-adenosylhomocysteine hydrolase [Homo sapiens] >pir A43629 A43629 adenosylhomocysteinase (EC 3.3.1.1) - human Length = 432	gi 178279	2	1372	98	98	HMWTV54	Lung, Pancreas, Prostate, Breast/Ovarian
218	828967	putative tRNA synthetase-like protein [Homo sapiens] >gi 4104935 (AF042347) putative phenylalanyl-tRNA synthetase alpha-subunit; PheHA [Homo sapiens] >sp E317305 E317305 PUTATIVE tRNA SYNTHETASE-LIKE PROTEIN. >sp G2102679 G2102679 PUTATIVE tRNA SYNTHETASE	gi 2102679	3	1535	98	98	HMUBT12	Pancreas, Prostate, Breast/Ovarian
219	828977	insulin-like growth factor binding protein 2 [Homo sapiens] >bbs 06618 insulin-like growth factor binding protein-2, IGF-BP-2 [human, placenta, Peptide, 328 aa] [Homo sapiens] >pir A41927 A41927 insulin-like growth factor-binding protein 2 precursor - hum	gi 179477	2	685	100	100	HMVAW27	Lung, Pancreas, Prostate, Breast/Ovarian

220	828978	annexin IV (placental anticoagulant protein II) [Homo sapiens] >gnl PID d1011889 annexin IV (carbohydrate-binding protein p33/41) [Homo sapiens] >pir A42077 A42077 annexin IV - human >sp P09525 ANX4_HUMAN ANNEXIN IV (LIPOCORTIN IV) (ENDONEXIN I) (CHROMOB	gij 178699	213	1184	100	100	HNTMH78	Lung, Pancreas, Prostate
221	828979			16	1080			IIMUBO53	Lung, Pancreas, Prostate, Colon, Breast/Ovarian
222	829001			1621	1959			IIMSR30	Lung, Pancreas, Prostate, Breast/Ovarian
223	829003	plasma gelsolin [Homo sapiens] >pir A03011 FAHUP gelsolin precursor, plasma - human >sp P06396 GELS_HUMAN GELSOLIN PRECURSOR, PLASMA (ACTIN- DEPOLYMERIZING FACTOR) (ADF) (BREVIN) (AGEL). >gnl PID e20565 plasma gelsolin (AA 49- 117) [Homo sapiens] {SUB 49-11	gij 736249	635	2536	99	99	IIMSKA53	Lung, Pancreas, Prostate
224	829016	(AB006625) The human homolog of a mouse imprinted gene, Peg3. [Homo sapiens] >sp P78418 P78418 KIAA0287 (PEG3) (FRAGMENT). >gij 1899244 PEG3 [Homo sapiens] {SUB 518-1132} Length = 1132	dbj AB006625_1	409	759	87	87	IIMI173	Prostate, Breast/Ovarian
225	829027	ras-like protein [Homo sapiens] >pir D34788 TVHUC4 transforming protein ras (teratocarcinoma clone TC10) - human Length = 213	gij 190881	2	577	100	100	IIMIBE59	Prostate, Colon

226	829028	RnudC gene product [Rattus norvegicus] >pir/A55897 A55897 protactin-induced T cell protein c15 - rat >sp Q63525 Q63525 C15 MRNA. Length = 332	g 619907	31	1110	95	98	HMG13Q36	Pancreas, Prostate, Breast/Ovarian
227	829031	protocadherin X [Mus musculus] >sp G4099553 G4099553 PROTOCADHERIN X. Length = 928	g 4099553	116	637	90	93	HMG13I69	Lung, Pancreas, Prostate, Breast/Ovarian
228	829034			28	1362			HME1Y69	Pancreas, Prostate
229	829036	Similar to B.subtilis Poly(A) polymerase (SW:PAPS_BACSU) [Caenorhabditis elegans] >sp Q93795 Q93795 F55B12.4 PROTEIN. Length = 440	gn PID e1347205	114	1151	67	81	LIME1J75	Pancreas, Prostate
230	829049	UDP-Gal:GlcNAc galactosyltransferase [Homo sapiens] >sp O60910 O60910 UDP-GAL:GLCNAC GALACTOSYLTRANSFERASE. Length = 393	gn PID e1283714	233	1444	94	94	HME1FQ33	Prostate, Colon
231	829073			193	843			HL YCD85	Pancreas, Prostate
232	829075			2	484			HMAAD66	Lung, Pancreas, Prostate, Breast/Ovarian
233	829076			3	665			HADDC41	Lung, Pancreas, Breast/Ovarian
234	829080			3	500			LIMABG80	Prostate, Breast/Ovarian
235	829087	small GTP-binding protein [Oryctolagus cuniculus] >pir/A48500 A48500 small GTP-binding protein Rab25 - rabbit Length = 213	g 436001	157	873	95	97	HL W13Y67	Pancreas, Prostate, Breast/Ovarian

236	829092	UDP-galactose translocator [Homo sapiens] >pir JC4903 JC4903 UDP-galactose transporter, splice form 1 - human Length = 393	gnl PID d1013353	1	513	85	85	HLW1BC74	Pancreas, Prostate
237	829095			3	425			HLW1BN189	Lung, Pancreas, Prostate, Colon, Breast/Ovarian
238	829096	antiquitin=26g turgor protein homolog [human, kidney, Peptide, 511 aa] [Homo sapiens] >pir A54676 A54676 antiquitin - human >sp I49419 DHAX_HUMAN ANTIQUITIN (EC 1.2.1.-), Length = 511	bbs 158840	552	1628	97	97	HLWAO28	Prostate, Breast/Ovarian
239	829118	nuclear autoantigen fo 14 kDa [Homo sapiens] >sp O43805 O43805 NUCLEAR AUTOANTIGEN FO 14 KDA, Length = 119	gnl PID e322419	2	415	99	99	HLSDA35	Lung, Prostate
240	829152	unknown protein precursor [Homo sapiens] >pir JN0596 JN0596 fibrinogen-related protein IIIFREP-1 precursor - human >sp Q08830 Q08830 FIBRINOGEN-LIKE PROTEIN 1 PRECURSOR, Length = 312	gnl PID d1003846	215	1231	95	95	HLICU82	Lung, Pancreas, Prostate
241	829160	ubiquitin-conjugating enzyme UbcH6 [Homo sapiens] Length = 193	gil1064914	2	769	83	83	HLFBI56	Lung, Pancreas, Prostate, Colon
242	829163			403	930			HSPBG80	Lung, Pancreas, Breast/Ovarian
243	829176	C4b-binding protein alpha chain [Homo sapiens] >gil190502 C4b-binding protein alpha chain [Homo sapiens] >pir A33568 NBHUC4 C4b-binding protein alpha chain precursor - human >sp P04003 C4BP_HUMAN C4B-BINDING PROTEIN ALPHA CHAIN PRECURSOR (PROLINE-RICH PRO	gil190500	3	662	100	100	HLQBR92	Lung, Pancreas
244	829204			515	913			HLISB22	Prostate, Breast/Ovarian

245	829207		111	977		HLISA66	Prostate, Breast/Ovarian	
246	829228		1	2508		HKGBQ77	Lung, Prostate, Colon	
247	829252		96	1322		HKAP121	Pancreas, Prostate	
248	829254		1	483		HKFB196	Lung, Pancreas, Prostate, Breast/Ovarian	
249	829269		121	474		HKALE96	Lung, Pancreas, Prostate, Colon, Breast/Ovarian	
250	829277		3	596		HIJPCG91	Lung, Prostate	
251	829290		100	207		HJBDL52	Lung, Pancreas, Prostate, Breast/Ovarian	
252	829294		3	1847		HISDU47	Pancreas, Prostate	
253	829299		3	794		HISFC32	Lung, Pancreas, Prostate	
254	829308	d11409.2 (Melanoma-Associated Antigen MAGL LIKE) [Homo sapiens] >sp O76058 O76058 D11409.2 (MELANOMA-ASSOCIATED ANTIGEN MAGL LIKE). Length = 606	207	938	47	70	HIHCN93	Lung, Pancreas, Prostate, Colon, Breast/Ovarian
255	829349	ribosomal protein S15a [Rattus norvegicus] >pir JC2234 JC2234 ribosomal protein S15a - rat Length = 130	152	547	100	100	HICAF44	Lung, Pancreas, Prostate, Breast/Ovarian
256	829354	RAD4 gene product [Saccharomyces cerevisiae] Length = 730	1	1113	44	65	HAJBD51	Lung, Pancreas, Breast/Ovarian

257	829388	DNase protein [Homo sapiens] >gi 1620214 XIB [Homo sapiens] >pir JC4633 JC4633 DNase I-like endonuclease (EC 3.1.-.-) - human >sp P49184 DRNL_HUMAN MUSCLE-SPECIFIC DNASE I-LIKE PRECURSOR (EC 3.1.21.-) (DNASE X) (XIB). Length = 302	gi 929628	319	1281	94	94	HUVCJ22	Lung, Pancreas, Colon, Breast/Ovarian
258	829340			258	437			HAPOU28	Lung, Pancreas, Colon, Breast/Ovarian
259	829626	mannosyl-oligosaccharide 1,2-alpha-mannosidase (EC 3.2.1.113) - rabbit (fragment) >gi 474282 mannosyl-oligosaccharide alpha-1,2-mannosidase [Oryctolagus cuniculus] (SUB 12-480) Length = 480	pir B54408 B54408	3	764	75	88	HCEES14	Lung, Pancreas, Colon, Breast/Ovarian
260	829730	underexpressed in thyroid tissue after TSH stimulation [Canis familiaris] >sp Q28283 Q28283 CSFW PROTEIN. Length = 343	gnl PDIe252512	455	1153	62	75	HAJBK53	Pancreas, Breast/Ovarian
261	829892	(AF033651) cellular apoptosis susceptibility protein [Homo sapiens] >sp O75432 O75432 CELLULAR APOPTOSIS SUSCEPTIBILITY PROTEIN. Length = 971	gi 3598795	64	1053	85	85	HAMFJ43	Lung, Prostate
262	829933	(AF035606) calcium binding protein [Homo sapiens] >sp O75340 O75340 CALCIUM BINDING PROTEIN. Length = 191	gi 3342794	1	540	86	86	HAICT76	Pancreas, Prostate
263	829938	(AF067855) geminin [Homo sapiens] >sp O75496 O75496 GEMININ. Length = 209	gi 3249005	230	952	93	93	HAIBS55	Pancreas, Prostate
264	829969			551	814			HACCB64	Lung, Pancreas, Prostate, Breast/Ovarian

265	829982	(AF020352) NADH:ubiquinone oxidoreductase 15 kDa IP subunit [Homo sapiens] >gi 3911482 (AF047434) NADH:ubiquinone oxidoreductase 15kDa subunit: Cl-15 protein [Homo sapiens] >sp O43920 NIPM_HUMAN NADH:UBIQUINONE OXIDOREDUCTASE 15 KD SUBUNIT (EC 1.6.5.3) (E	gi 2655055	28	399	100	100	11ARCI:25	Prostate, Breast/Ovarian
266	830007	catechol-O-methyltransferase [Homo sapiens] >gi 403304 catechol O-methyltransferase [Homo sapiens] >pir S37406 A38459 catechol O-methyltransferase (EC 2.1.1.6) - human >sp P21964 COMT_HUMAN CATECHOL O-METHYLTRANSFERASE, MEMBRANE-BOUND FORM (EC 2.1.1.6) (M	gi 180920	110	1006	99	99	H6EDW66	Lung, Prostate, Breast/Ovarian
267	830019	(AF030249) putative dienoyl-CoA isomerase [Homo sapiens] >gi 564065 peroxisomal enoyl-CoA hydratase-like protein [Homo sapiens] >pir 38882 38882 peroxisomal enoyl-CoA hydratase-like protein - human >sp Q13011 ECH1_HUMAN PROBABLE PEROXISOMAL ENOYL-COA HY	gi 2623168	77	976	94	96	I12MAC92	Prostate, Breast/Ovarian
268	830073			1	690			HBW/BK27	Lung, Pancreas, Breast/Ovarian
269	830130			1	177			H2LAD55	Lung, Prostate, Breast/Ovarian
270	830134			16	1290			H2CBP53	Lung, Pancreas, Prostate, Colon, Breast/Ovarian

271	830135	neutrophil gelatinase associated lipocalin [Homo sapiens] >sp P80188 NGAL_HUMAN NEUTROPHIL GELATINASE-ASSOCIATED LIPOCALIN PRECURSOR (NGAL) (P25) (25 KDa) ALPHA-2-MICROGLOBULIN-RELATED SUBUNIT OF MMP-9 (LIPOCALIN-2) (ONCOGENE 24P3). Length = 198	gi 929657	2	763	100	100	H2MAC06	Pancreas, Prostate, Breast/Ovarian
272	830148	snRNP polypeptide B [Homo sapiens] >sp Q15182 Q15182 SNRNP POLYPEPTIDE B. Length = 285	gi 190247	96	839	79	79	HAICK77	Lung, Prostate, Breast/Ovarian
273	830149	threonyl-tRNA synthetase [Homo sapiens] >pir A38867 YSHUT threonine--tRNA ligase (EC 6.1.1.3) - human Length = 712	gi 1464742	3	2333	95	95	H2C13C04	Lung, Pancreas, Prostate
274	830154	spectrin SH3 domain binding protein 1 [Homo sapiens] >sp O76049 O76049 SPECTRIN SH3 DOMAIN BINDING PROTEIN 1. Length = 508	gi 165429	2	1081	100	100	HYAAC49	Lung, Pancreas
275	830183	heat shock protein 84 - mouse >pir B34461 B34461 heat shock protein 90 beta - rabbit (fragment) (SUB I-25) >sp P30947 HS9B_RABIT HEAT SHOCK PROTEIN HSP 90-BETA (HSP 84) (FRAGMENT). (SUB 2-25) >pir S13268 S13268 heat shock protein, 90K - bovine (fragment)	pir A35569 HHMS84	92	358			HW1.QF08	Pancreas, Breast/Ovarian
276	830194	heat shock protein 84 - mouse >pir B34461 B34461 heat shock protein 90 beta - rabbit (fragment) (SUB I-25) >sp P30947 HS9B_RABIT HEAT SHOCK PROTEIN HSP 90-BETA (HSP 84) (FRAGMENT). (SUB 2-25) >pir S13268 S13268 heat shock protein, 90K - bovine (fragment)	pir A35569 HHMS84	3	1043	100	100	H1LDC120	Lung, Pancreas, Breast/Ovarian
277	830207	(AF016437) contains similarity to a C2H2-type zinc finger [Caenorhabditis elegans] >sp O16350 O16350 F13H6.1 PROTEIN. Length = 631	gi 2315332	173	1051	45	63	HWLMF07	Pancreas, Colon
278	830242			85	654			HW1.UF58	Lung, Pancreas



279	830328	putative cyclin G1 interacting protein [Homo sapiens] >sp O43257 O43257 PUTATIVE CYCLIN G1 INTERACTING PROTEIN. Length = 154	gi 2668505	304	954	81	81	HWLEL26	Lung, Colon, Breast/Ovarian
280	830340	putative cell surface antigen [Rattus norvegicus] >sp P9788 P9788 PUTATIVE CELL SURFACE ANTIGEN. Length = 547	gi 1890275	1	336	63	81	HWLEG68	Pancreas, Colon
281	830341	peroxisomal acyl-coenzyme A oxidase, AOX [human, liver, Peptide, 661 aa] [Homo sapiens] Length = 661	bbs 144907	1	648	100	100	HSIA1179	Lung, Pancreas
282	830351			3	656			HWHQI21	Colon, Breast/Ovarian
283	830358			456	716			HSUAE53	Lung, Colon, Breast/Ovarian
284	830390	platelet membrane glycoprotein IIIa beta subunit [Homo sapiens] >sp O15495 O15495 PLATELET MEMBRANE GLYCOPROTEIN IIIA BETA SUBUNIT. Length = 784	gi 2443452	2	523	90	90	HWGQA69	Pancreas, Colon
285	830400	phosphate carrier protein [Homo sapiens] >pir B53737 B53737 phosphate carrier protein, form B - human Length = 361	gi 38262	2	1078	99	100	HW1IPY68	Lung, Pancreas, Breast/Ovarian
286	830437	IgG Fc receptor I [Homo sapiens] >gi 292169 Fc gamma receptor I [Homo sapiens] >pir A39878 A39878 Fc gamma (IgG) receptor I-A (high affinity) precursor - human >sp Q92663 Q92663 FC GAMMA RECEPTOR I. Length = 374	gi 180279	3	1199	91	91	HWABG32	Lung, Colon

287	830458	HBp15/L22 [Sus scrofa] >gnl PID d1005074 HBp15/L22 [Mus musculus] >pir JC2121 JC2121 heparin-binding protein 15 - pig >pir JC2119 JC2119 heparin-binding protein 15 - mouse Length = 128	gnl PID d1005075	1	441	70	70	HDQMF96	Lung, Pancreas
288	830466	tenascin X [Homo sapiens] >sp P78530 P78530		988	1260			HOEIZ61	Lung, Colon
289	830497	TENASCIN X (TENASCIN-X). >gil2347137 (AF019413) tenascin X [Homo sapiens] {SUB 2591-4289} >pir A42175 A42175 tenascin homolog 3.9kF3-3 - human (fragment) {SUB 2793-2880} >pir 342175 B42175 tenascin homolog 3.9kF	gil1841546	2	1531	99	99	HUFBX52	Lung, Breast/Ovarian
290	830511	carcinoembryonic antigen [Homo sapiens] >gil178677 carcinoembryonic antigen precursor [Homo sapiens] >pir A36319 A36319 carcinoembryonic antigen precursor - human >sp P06731 CCEM_HUMAN CARCINOEMBRYONIC ANTIGEN PRECURSOR (CEA) (MECONIUM ANTIGEN 100) (CD66E	gil180223	3	1292	99	99	HWLGV67	Pancreas, Colon
291	830512	carcinoembryonic antigen [Homo sapiens] >gil178677 carcinoembryonic antigen precursor [Homo sapiens] >pir A36319 A36319 carcinoembryonic antigen precursor - human >sp P06731 CCEM_HUMAN CARCINOEMBRYONIC ANTIGEN PRECURSOR (CEA) (MECONIUM ANTIGEN 100) (CD66E	gil180223	3	2213	87	89	HUFC129	Lung, Pancreas

292	830513		3	215		IIPRTG72	Lung, Colon, Breast/Ovarian
293	830540	protein kinase MUK2 [Rattus norvegicus] >gi2772514 serine/threonine protein kinase [Rattus norvegicus] >spP35465IPAK1_RAT SERINE/THREONINE-PROTEIN KINASE PAK- ALPHA (EC 2.7.1.-) (P68-PAK) (P21- ACTIVATED KINASE) (ALPHA-PAK) (PROTEIN KINASE MUK2). Length	2	733	100	HTLHR67	Lung, Pancreas, Colon
294	830550	guanine nucleotide-binding regulatory protein-beta- 2 subunit [Homo sapiens] >gi339935 transducin beta-2 subunit [Homo sapiens] >gi3135310 (AF053356) GNB2 [Homo sapiens] >pirB26617IRGHUB2 GTP-binding regulatory protein beta-2 chain - human >spP11016IGB	3	500	100	HTWJC08	Lung, Breast/Ovarian
295	830567		141	377		HTTBH33	Lung, Pancreas
296	830586	(2'-5')oligoadenylate synthetase [Homo sapiens] Length = 364	2	1192	98	HKACP86	Pancreas, Prostate, Breast/Ovarian
297	830632	P2 gene for c subunit of mitochondrial ATP synthase gene product [Homo sapiens] >gnlPIDd1002921 ATP synthase subunit c precursor [Homo sapiens] >pirS34067S34067 H+- transporting ATP synthase (EC 3.6.1.34) lipid- binding protein P2 precursor, mitochondri	264	803	85	HTPCV95	Lung, Breast/Ovarian

298	830645	propionyl CoA carboxylase beta subunit, beta PCC {EC 6.4.1.3} [human, liver, placenta, HL 1008, Peptide, S39 aa] [Homo sapiens] >pir A53020 A53020 propionyl-CoA carboxylase {EC 6.4.1.3} beta chain precursor - human >gil 3036995 propionyl-CoA carboxylase B	bbs 40816	54	1505	99	99	HTEDS58	Lung, Pancreas, Colon
299	830652	strong homology to human RING3 sequence [Homo sapiens] >sp O60885 O60885 HUNK1 MRNA. Length = 722	gnl PID e1290115	1	177	64	64	HUKFL74	Lung, Colon
300	830659	CDC42 GTP-binding protein [Canis familiaris] >gil 183490 GTP-binding protein G25K [Homo sapiens] >gil 293321 CDC42Mm [Mus musculus] >gil 1049309 CDC42 protein [Mus musculus] >pir A39265 A39265 GTP-binding protein G25K, placental - human >pir S57563 S57563 CD	gil 887408	118	714	100	100	HKAOE74	Lung, Pancreas, Breast/Ovarian
301	830696			2	514			HSTBJ95	Lung, Breast/Ovarian
302	830706			2457	2909			HELFG05	Pancreas, Breast/Ovarian
303	830743	ATP SYNTHASE EPSILON CHAIN, MITOCHONDRIAL (EC 3.6.1.34). Length = 50	sp P56381 A1TPE_HUMAN	53	262	100	100	HCBBA51	Lung, Colon
304	830770	p21-activated protein kinase [Homo sapiens] >pir S58682 S58682 protein kinase, p21-activated (EC 2.7.1.-) - human Length = 525	gil 780808	1	498	99	99	HEMCG27	Lung, Colon, Breast/Ovarian
305	830830	(AF002822) cyclin B2 [Homo sapiens] >sp G4101270 G4101270 CYCLIN B2. Length = 398	gil 4101270	99	1358	99	99	HRUCI57	Lung, Pancreas, Colon

306	830838		1	747		HS2AF59	Lung, Pancreas, Colon, Breast/Ovarian
307	830851		2	718		HTXLJ25	Pancreas, Colon
308	830853		2	1183		1HRDSS42	Pancreas, Colon
309	830856		542	874		1ISAAX81	Colon, Breast/Ovarian
310	830862	ribosomal protein [Homo sapiens] >gi453281 ribosomal protein S23 [Rattus norvegicus] >pir[S41955]S41955 ribosomal protein S23, cytosolic - rat >pir[S42105]S42105 ribosomal protein S23, cytosolic - human >pir[S2292]S2292 ribosomal protein S23 - rat >gnt	gnl P D d1003910	518	100	111JLC05	Lung, Prostate, Breast/Ovarian
311	830879	(AJ002120) Zfx [Monodelphis domestica] >sp O19019 O19019 ZFX TYPE GENE (FRAGMENT). Length = 180	gnl P D e354749	592	39	HVAAB82	Pancreas, Colon
312	830919		69	536		HOUHK65	Pancreas, Breast/Ovarian
313	830969	(AF005046) serine/threonine kinase [Homo sapiens] >gnt P D e1371371 (AJ011855) PAK4 protein [Homo sapiens] >sp G4101587 G4101587 SERINE/THREONINE KINASE. Length = 591	gi4101587	514	96	HOGAU20	Pancreas, Breast/Ovarian
314	830991	insulin-like growth factor-binding protein [Homo sapiens] >gi386791 growth factor-binding protein- 3 [Homo sapiens] >gi398164 insulin-like growth factor binding protein 3 [Homo sapiens] >pir A36578 OHU3 insulin-like growth factor- binding protein 3 precu	gi183116	607	86	HDLAE73	Pancreas, Breast/Ovarian

315	831002	cyclin [Homo sapiens] >gi 387005 proliferating cell nuclear antigen (PCNA) [Homo sapiens] >pir A27445 WMHUET proliferating cell nuclear antigen - human >sp P12004 PCNA_HUMAN PROLIFERATING CELL NUCLEAR ANTIGEN (PCNA) (CYCLIN). Length = 261	gi 181272	168	974	100	100	HOEMJ36	Colon, Breast/Ovarian
316	831003	T-plastin - human >sp P13797 PLST_HUMAN T-PLASTIN. {SUB 4-630} >gi 190028 T-plastin polypeptide [Homo sapiens] {SUB 61-630} >gi 339848 T-plastin [Homo sapiens] {SUB 1-143} >gi 292832 T-plastin [Homo sapiens] {SUB 588-630} Length = 630	pir A34789 A34789	91	2007	94	95	HAIBD64	Lung, Pancreas
317	831021			474	662			HE8BN45	Pancreas, Colon, Breast/Ovarian
318	831036	(A1006068) dTDP-D-glucose 4,6-dehydratase [Homo sapiens] >sp E1363774 E1363774 DTDP-D-GLUCOSE 4,6-DEHYDRATASE (EC 4.2.1.46). Length = 350	gnl PID e1363774	1	621	100	100	HNTSQ61	Pancreas, Colon
319	831071	lrp gene product [Homo sapiens] >pir S5723 S5723 lrp protein - human >sp Q14764 MVP_HUMAN MAJOR VAULT PROTEIN (MVP) (LUNG RESISTANCE-RELATED PROTEIN). Length = 896	gi 895840	67	2610	94	94	HWLEG93	Lung, Pancreas
320	831094			755	928			IINFEO67	Colon, Breast/Ovarian

321	831099	fibronectin receptor beta subunit precursor (AA -20 to 778) [Homo sapiens] >pir B27079 B27079 fibronectin receptor beta chain precursor - human >sp P05556 TBI_HUMAN FIBRONECTIN RECEPTOR BETA SUBUNIT PRECURSOR (INTEGRIN BETA-1) (CD29) (INTEGRIN VLA-4 BETA	gi 31442	3	1697	99	100	HLA3AB03	Lung, Pancreas, Colon, Breast/Ovarian
322	831113	4E-binding protein 1 [Homo sapiens] >pir S50866 S50866 4E-BP1 protein - human >pir JC5899 JC5899 initiation factor 4E-binding protein 1 - human >sp Q13541 Q13541 4E- BINDING PROTEIN 1. Length = 118	gi 561630	1	414	100	100	HMWHIP74	Lung, Pancreas, Colon, Breast/Ovarian
323	831120	Similarity to Human hnRNP F protein (PIR Acc. No. S43484):	gn P D c 349655	1	1221			HWLHY12	Pancreas, Colon
324	831172	(AF042501) cytochrome b [Homo sapiens] >sp O78829 O78829 CYTOCHROME B (FRAGMENT). Length = 380	gi 3372365	2	721	52	66	HLWBE22	Pancreas, Breast/Ovarian
325	831178			512	829	69	70	HDLAC61	Lung, Colon
326	831184			770	1399			HWLGP91	Lung, Pancreas, Colon
327	831203			3	545			HMLCQ42	Pancreas, Colon, Breast/Ovarian
328	831210	TGF-beta masking protein large subunit [Rattus norvegicus] >pir A38261 A38261 masking protein precursor - rat Length = 1712	gi 207286	1	498	86	91	HMEU62	Pancreas, Colon
329	831228			104	214			HMEAM30	Lung, Pancreas, Breast/Ovarian

330	831256	MLN 64 [Homo sapiens] >dbj D38255_1 CAB1 [Homo sapiens] >pir I38027 I38027 MLN 64 protein - human >sp Q14849 Q14849 MLN64 MRNA. Length = 445	gi 951279	658	1164	94	94	HMTBL29	Lung, Pancreas
331	831257	MLN 64 [Homo sapiens] >dbj D38255_1 CAB1 [Homo sapiens] >pir I38027 I38027 MLN 64 protein - human >sp Q14849 Q14849 MLN64 MRNA. Length = 445	gi 951279	323	862	91	91	HILWDQ05	Pancreas, Colon
332	831277			3	1310			HUTHD56	Lung, Pancreas, Colon
333	831317	inter-alpha-trypsin inhibitor light chain [Homo sapiens] >gi 32047 HC polypeptide [Homo sapiens] >gi 24479 precursor polypeptide [Homo sapiens] >gi 825614 alpha1-microglobulin [Homo sapiens] >pir S13433 HCHU alpha-1-microglobulin/inter- alpha-trypsin inhib	gi 186600	193	1290	100	100	HILQAC21	Pancreas, Breast/Ovarian
334	831339	(AB012276) ATFX [Mus musculus] >sp O70191 O70191 ATFX (FRAGMENT). >sp G246896 G246896 ATFX=ATF4 RELATED PROTEIN. {SUB 1-37} >sp G246899 G246899 ATFX=ATF4-RELATED PROTEIN. {SUB 38- 76} Length = 84	gn P1D1d 026241	631	1029	90	93	HLICC93	Lung, Colon, Breast/Ovarian
335	831363	acyl coenzyme A:cholesterol acyltransferase, carboxylesterase, ACAT {EC 2.3.1.26} [human, liver, Peptide, 568 aa] [Homo sapiens] >sp G415564 G415564 CARBOXYLESTERASE {EC 3.1.1.1}. {SUB 20-568} >gi 179930 carboxylesterase [Homo sapiens] {SUB 62-568} Length	bbs 156481	123	1871	98	98	HLDNR55	Lung, Colon



336	831367	D-dopachrome tautomerase [Homo sapiens] >gi1864028 D-dopachrome tautomerase [Homo sapiens] >gi3047378 (AF058293) D-dopachrome tautomerase [Homo sapiens] >gi1101354 phenylpyruvate tautomerase II [Homo sapiens] >gi2352915 (AF012434) D-dopachrome ta	gi1805303	325	618	100	100	III.DDR74	Lung, Colon
337	831379	cDNA from hypercalcemic tumour [Rattus norvegicus] >pirS28223 S28223 parathyroid hormone-like protein - rat >spQ05310 L10K_RAT LEYDIG CELL TUMOR 10 KD PROTEIN. Length = 93	gi157064	3	383	90	95	HKQAC03	Lung, Pancreas, Colon, Breast/Ovarian
338	831385			96	377			HKIMC75	Lung, Pancreas, Colon, Breast/Ovarian
339	831390	aldehyde reductase (EC 1.1.1.2) [Homo sapiens] >gi2707824 (AF036683) aldehyde reductase [Homo sapiens] >pirA33851 A33851 alcohol dehydrogenase (NADP+) (EC 1.1.1.2) - human >spG2707824 G2707824 ALDEHYDE REDUCTASE - >spP14550 ALDX_HUMAN ALCOHOL DEHYDROGE	gi178481	254	1312	94	94	HKC10F04	Lung, Pancreas

340	831391	islet regenerating protein [Homo sapiens] >pirA35197 RGH1A regenerating islet lectin I- alpha precursor - human >spP0545 ILITA_HUMAN LITHOSTATHINE I ALPHA PRECURSOR (PANCREATIC STONE PROTEIN) (PSP) (PANCREATIC TIREAD PROTEIN) (PTP) (ISLET OF LANGERHANS	gil190979	71	592	100	100	HLDBE06	Pancreas, Colon
341	831405	factor H homologue [Homo sapiens] >pir156100 156100 factor H homologue - human >spQ03591 CFH1_HUMAN COMPLEMENT FACTOR H-LIKE PROTEIN 1 PRECURSOR (H36). Length = 330	gil183763	53	1078	94	94	HLDOB31	Lung, Pancreas, Colon, Breast/Ovarian
342	831442	PDGF associated protein [Homo sapiens] >spQ13442 IP28_HUMAN 28 KD HEAT- AND ACID-STABLE PHOSPHOPROTEIN (HASPP28) (PDGF ASSOCIATED PROTEIN). Length = 181	gil136584	2	593	60	60	HKAEB15	Lung, Pancreas, Colon, Breast/Ovarian
343	831476	dermatopontin [Homo sapiens] >pirA47220 A47220 dermatopontin precursor - human >spQ07507 DERM_HUMAN DERMATOPONTIN PRECURSOR. >pirS34838 S34838 tyrosine-rich acidic matrix protein - pig {SUB 101-144} Length = 201	gil11614	1	630	91	91	HJMBK21	Lung, Pancreas, Colon
344	831488	similar to Saccharomyces cerevisiae Sp14; protein has potential N-terminal zinc-finger [Homo sapiens] >gil1401053 SUPT4H [Homo sapiens] >gil1401055 SUPT4H [Homo sapiens] >gil1401066 Sup14h [Mus musculus] >gil3779194 chromatin structural protein homolog [M	gil1209779	158	580	100	100	HJBCG39	Colon, Breast/Ovarian

345	831518		240	467		HATCV09	Pancreas, Colon, Breast/Ovarian
346	831519	(AF062536) cullin 1 [Homo sapiens] >sp Q60719 O60719 CULLIN 1. >gi 4153866 (AC005229) cullin 1 [Homo sapiens] {SUB 1-263} Length = 776	gi 3139077	165	1712	100	100 Pancreas, Breast/Ovarian
347	831521		3	863		HIBCE91	Colon, Breast/Ovarian
348	831550	mel-13a protein - mouse Length = 132	pir S65785 S65785	158	457	70	75 Lung, Pancreas, Breast/Ovarian
349	831560		1474	1818		HCROA68	Pancreas, Breast/Ovarian
350	831562	Fibromodulin [Homo sapiens] >sp Q06828 FMOD_HUMAN FIBROMODULIN PRECURSOR (FM) (COLLAGEN-BINDING 59 KD PROTEIN). Length = 376	gi 297091	28	1272	90	91 Pancreas, Breast/Ovarian
351	831570	(AF042822) epithin [Mus musculus] >sp G4104970 G4104970 EPITHIN. Length = 902	gi 4104970	2	1861	77	85 Lung, Pancreas, Colon
352	831593		726	878		HIBFW28	Lung, Pancreas
353	831596	32 kd accessory protein [Bos taurus] >gi 190376 proton A TPase accessory subunit [Homo sapiens] {SUH 264-351} Length = 351	gi 736727	2	808	100	100 Colon, Breast/Ovarian
354	831627		1	903		HBJH146	Lung, Pancreas
355	831649		1	738		HFTDD09	Lung, Colon
356	831664	transformation upregulated nuclear protein - human Length = 464	pir S43363 S43363	180	1574	94	94 Lung, Colon

357	831674	complement protein C8 beta subunit precursor [Homo sapiens] >pir A4307 C8HUB complement C8 beta chain precursor - human >sp P07358 C08B_HUMAN COMPLEMENT COMPONENT C8 BETA CHAIN PRECURSOR. Length = 591	gi 1197720	1	1338	96	96	HLDX36	Pancreas, Colon
358	831684	(AF053630) monocyte/neutrophil elastase inhibitor [Homo sapiens] >pir S27383 S27383 elastase inhibitor - human >sp P30740 ILEU_HUMAN LEUKOCYTE ELASTASE INHIBITOR (LEI) (MONOCYTE/NEUTROPHIL ELASTASE INHIBITOR) (EI). >sp G2997692 G2997692 MONOCYTE/NEUTROPHIL	gi 2997692	1	1311	96	96	HFOX22	Pancreas, Colon
359	831687	Mpv17 [Mus musculus] >pir S29031 S29031 mpv17 protein - mouse >sp P19258 MPV1_MOUSE MPV17 PROTEIN. >gi 3252875 (AF038632) Mpv17 protein [Mus musculus] (SUB 155-176) Length = 176	gi 199790	60	305	89	93	HPKHD75	Pancreas, Colon
360	831726	rat ribosomal protein L36 [Rattus norvegicus] >pir JN0483 JN0483 ribosomal protein L36 - rat Length = 105	gi 312345	77	454	98	98	HAGDQ96	Lung, Breast/Ovarian
361	831736			95	484			HLWEQ18	Colon, Breast/Ovarian
362	831762	ear-2 gene product [Homo sapiens] >pir S02709 S02709 ear-2 protein - human >sp P10588 EAR2_HUMAN V-ERBA RELATED PROTEIN EAR-2. Length = 403	gi 31065	37	720	76	77	HEQB179	Pancreas, Colon
363	831801			3	812			HKAHD85	Lung, Pancreas, Breast/Ovarian

364	831848		2018	2284		HE8AF82	Lung, Colon, Breast/Ovarian
365	831861	(AF076786) serum amyloid A-activating factor SAF-8 [Oryctolagus cuniculus] >sp G3986442 G3986442 SERUM AMYLOID A- ACTIVATING FACTOR SAF-8 (FRAGMENT). Length = 214	341	775	77	HLPCX51	Lung, Pancreas, Breast/Ovarian
366	831866	(AF034174) histone macroH2A1.2 [Homo sapiens] >sp G3341992 G3341992 HISTONE MACROH2A1.2. Length = 371	53	1186	100	HE6FG90	Lung, Colon
367	831878		2	661		HD7LN67	Colon, Breast/Ovarian
368	831899		1	693		HD7BQ51	Colon, Breast/Ovarian
369	831913	nuclear antigen H731 [Homo sapiens] >pir J5193 J5193 nuclear protein H731 - human >sp Q99834 Q99834 NUCLEAR ANTIGEN H731. Length = 438	95	1132	96	HL_YG_A31	Lung, Colon
370	831972	p619 [Homo sapiens] >pir S71752 S71752 giant protein p619 - human >sp Q15751 Q15751 P619. Length = 4861	331	855	33	HDHKK57	Lung, Pancreas, Breast/Ovarian
371	831985		425	805		HDPPF36	Lung, Pancreas, Colon, Breast/Ovarian
372	831986		30	467		HLIC168	Pancreas, Colon, Breast/Ovarian
373	832010	(AL021918) b3418.1 (Kruppel related Zinc Finger protein 184) [Homo sapiens] >sp O60792 O60792 B3418.1 (KRUPPEL RELATED ZINC FINGER PROTEIN 184). Length = 751	1	348	57	HDFTB44	Lung, Pancreas, Colon

374	832016	C protein (AA 1-159) [Homo sapiens] >pir S01387 S01387 UI snRNP protein C - human Length = 159	g i 37543	2	604	100	100	HTTDG34	Lung, Breast/Ovarian
375	832041	metalloelastase HME (EC 3.4.24.-) - human >sp P39900 COGM_HUMAN MACROPHAGE METALLOELASTASE PRECURSOR (EC 3.4.24.65) (HME) (MATRIX METALLOPROTEINASE-12) (MMP-12). Length = 470	pir A49499 A49499	54	1472	100	100	HDPGC33	Lung, Pancreas, Colon
376	832044	5-aminimidazole-4-carboxamide-1-beta-D- ribofuranoside transferase/inosinase [Homo sapiens] >gnl P D d1022617 5-aminimidazole-4- carboxamide ribonucleotide transferase [Homo sapiens] >pir JC4642 JC4642 purH bifunctional enzyme - human >sp Q13856	gnl P D d1012226	1	1794	99	99	HGCCOL40	Lung, Pancreas, Colon, Breast/Ovarian
377	832049	proteasome subunit HsC10-II [Homo sapiens] >pir S55041 S55041 multicatalytic endopeptidase complex (EC 3.4.99.46) beta chain C10-II - human >sp P49720 PRCT_HUMAN PROTEASOME THIETA CHAIN (EC 3.4.99.46) (MACROPAIN THIETA CHAIN) (MULTICATALYTIC ENDOPEPTIDASE C	gnl P D d1006190	84	710	99	100	HCFAU68	Lung, Pancreas, Breast/Ovarian
378	832122			427	846			HCUDT18	Lung, Pancreas, Colon, Breast/Ovarian
379	832148			246	380			HF1HN81	Colon, Breast/Ovarian
380	832197			433	642			HICQA1151	Pancreas, Breast/Ovarian
381	832237			290	553			HOCTE23	Lung, Colon
382	832246			66	959			HCM5D61	Lung, Pancreas

383	832256	ligand for eph-related receptor tyrosine kinases [Homo sapiens] >gi 1809292 putative EPH-related PTK receptor ligand LERK-8 [Homo sapiens] >sp Q15768 EFB3_HUMAN EPHRIN-B3 PRECURSOR (EPH-RELATED RECEPTOR TYROSINE KINASE LIGAND 8) (LERK-8) (EPH-RELATED RECE	gi 1469782	1	81	100	100	HBXAC19	Pancreas, Colon, Breast/Ovarian
384	832280	(AF071747) topoisomerase II alpha [Homo sapiens] >sp G3869316 G3869316 TOPOISOMERASE II ALPHA. Length = 1531	gi 3869316	2	1141	79	79	INTSQ37	Lung, Colon, Breast/Ovarian
385	832285			1550	1783			HLTBQ50	Lung, Prostate
386	832294			1	666			HBMCR80	Lung, Colon
387	832326			472	1131			HJPAT43	Lung, Colon, Breast/Ovarian
388	832333	CENP-B protein [Ovis aries] >sp P49451 CENB_SHEEP MAJOR CENTROMERE AUTOANTIGEN B (CENTROMERE PROTEIN B) (CENP-B) (FRAGMENT). Length = 239	gi 1016292	3	551	96	96	HCHMS55	Pancreas, Breast/Ovarian
389	832346			295	471			HBAQU45	Colon, Breast/Ovarian
390	832370	HER2 receptor [Homo sapiens] >gi 553282 c-erb-2 protein [Homo sapiens] (SUB 737-1031) >gi 553332 HER-2/neu [Homo sapiens] (SUB 1- 191) >gi 183989 HER2 receptor (AA at 3) [Homo sapiens] (SUB 740-910) >gi 182169 c-erb B2/neu protein [Homo sapiens] (SUB 1081-	gi 306840	2	406	83	83	HPIEC83	Lung, Breast/Ovarian
391	832381			138	539			HATAA19	Pancreas, Breast/Ovarian

392	832394	platelet-endothelial tetraspan antigen 3 [Homo sapiens] >sp P48509 C151_HUMAN PLATELET- ENDOTHELIAL TETRASPAN ANTIGEN 3 (PETA-3) (GP27) (MEMBRANE GLYCOPROTEIN SFA-1) (CD151 ANTIGEN). Length = 253	gi 341613	2	847	85	85	85	HF1TD21	Lung, Pancreas
393	832454	precursor polypeptide [Homo sapiens] >pir A25971 C2HU complement C2 precursor - human >gi 187765 MHC complement component C2 [Homo sapiens] {SUB 21-46} Length = 752	gi 34628	160	357	100	100	100	HLQB144	Prostate, Breast/Ovarian
394	832465	X box binding protein-1 [Homo sapiens]		1	324				HAIJC51	Lung, Pancreas
395	832475	>pir A36299 A36299 transcription factor hXBP-1 - human Length = 260	gi 306893	470	817	100	100	100	HTMJ52	Pancreas, Breast/Ovarian
396	832495	EB1 [Homo sapiens] >pir I52726 I52726 EB1 - human >sp Q15691 Q15691 EB1. Length = 268	gi 998357	1	933	100	100	100	IIAIDB85	Lung, Pancreas
397	832498	pyroline-5-carboxylate synthase [Homo sapiens] >sp G4097816 G4097816 PYRROLINE-5- CARBOXYLATE SYNTHASE. Length = 793	gi 4097816	2	1036	95	95	95	HLTGQ24	Lung, Pancreas
398	832501			736	996				HAGFI57	Lung, Pancreas, Colon
399	832505	protein synthesis factor [Homo sapiens] >sp P47813 P47813 HUMAN EUKARYOTIC TRANSLATION INITIATION FACTOR 1A (EIF- 1A) (EIF-4C). {SUB 2-144} Length = 144	gi 306725	61	648	100	100	100	HRA3V57	Lung, Pancreas, Prostate
400	832539	protein synthesis initiation factor 4A [Mus musculus] Length = 408	gi 673433	472	1125	93	93	93	HRABO69	Lung, Breast/Ovarian
401	832554	ILKCN1 [Homo sapiens] >sp Q99736 Q99736 ILKCN1 (FRAGMENT). Length = 1928	gi 2282576	409	927	99	99	99	ILK1CX71	Pancreas, Breast/Ovarian



402	832569	(AL023777) ma binding protein	2	667		HFCAE43	Lung, Colon
403	832578	[Schizosaccharomyces pombe] >sp O74978 O74978 RNA BINDING PROTEIN. Length = 276	123	936	64	HBBD67	Pancreas, Colon, Breast/Ovarian
404	832615		630	992		H2C8K94	Lung, Colon
405	832620		190	297		H2C8G53	Colon, Breast/Ovarian
406	832632	(AC002388) 60S ribosomal protein L30 iso[log [Arabidopsis thaliana] >sp O22165 O22165 60S RIBOSOMAL PROTEIN L30 ISOLOG. Length = 159	41	592	69	H2C8D94	Lung, Colon, Breast/Ovarian
407	832633	putative phospho-beta-glucosidase; [Bacillus stearothermophilus] >pir D49898 D49898 cellobiose phosphorylase system celC - Bacillus stearothermophilus >sp Q45401 Q45401 PUTATIVE PHOSPHO-BETA-GLUCOSIDASE. Length = 245	3	566	64	HWACF51	Pancreas, Breast/Ovarian
408	833483		2	604		HCTCK33	Lung, Breast/Ovarian
409	834574	similar to S. cerevisiae longevity-assurance protein 1 (Sp:P38703) [Caenorhabditis elegans] >sp Q17870 Q17870 SIMILAR TO S. CEREVISIAE LONGEVITY-ASSURANCE PROTEIN 1. Length = 362	634	1431	59	HHB126	Lung, Pancreas, Colon, Breast/Ovarian
410	834859	acidic calponin [human, kidney, Peptide, 329 aa] [Homo sapiens] >pir JC4501 JC4501 acidic calponin - human >sp Q15417 Q15417 ACIDIC CALPONIN. Length = 329	53	541	100	HSTA170	Lung, Pancreas, Colon, Breast/Ovarian

411	834861	factor activating exoenzyme S [Bos taurus] >gi189953 phospholipase A2 [Homo sapiens] >gi1899459 14-3-3 protein [Homo sapiens] >pirA38246PSHUAM 14-3-3 protein zeta - human >pirA47389[A47389 14-3-3 protein zeta - bovine >sp P29312 43Z_HUMAN 14-3-3 PROT	gil163042	74	967	99	99	99	HBXFL41	Lung, Pancreas, Prostate, Breast/Ovarian
412	834890	TRANSCRIPTION FACTOR BTF3 (RNA POLYMERASE B TRANSCRIPTION FACTOR 3). Length = 204	sp Q64152 BTF3_M OUSE	70	588	90	91	91	112CBT12	Lung, Pancreas, Prostate, Breast/Ovarian
413	835079			151	348				HOELH62	Lung, Pancreas, Breast/Ovarian
414	835554	homologue to sec61 [Rattus rattus] Length = 476	gi 206886	121	1287	98	98	98	HOHBI04	Lung, Pancreas
415	835560	immunoglobulin M heavy chain [Homo sapiens]		2	574				HE9NK60	Lung, Pancreas
416	835723	>gi38408 immunoglobulin M heavy chain [Homo sapiens] >pir[S37768]S37768 Ig mu chain C region - human Length = 453	gi 38406	48	1421	100	100	100	HLIFY90	Lung, Pancreas, Prostate, Colon, Breast/Ovarian
417	835791	(AJ005890) JM1 [Homo sapiens] >sp O60826 O60826 JM1 PROTEIN, COMPLETE CDS (CLONE LLNLC110M0111Q7 (RZPD BERLIN))AND LI.NLCL110K2140Q7 (RZPD BERLIN)). Length = 627	gn P1D1e1289743	437	1177	87	87	87	HTXJH25	Pancreas, Breast/Ovarian
418	835817			1369	1554				HAAJAZ17	Lung, Breast/Ovarian
419	835840			2	730				HHEOJ47	Lung, Pancreas
420	836048			2052	2276				IIDQDV21	Lung, Prostate

421	836898	human P5 [Homo sapiens] >pir C4369 C4369 P5 protein - human >sp Q15084 ERP5_HUMAN PROBABLE PROTEIN DISULFIDE ISOMERASE P5 PRECURSOR (EC 5.3.4.1). Length = 440	gnl PID cl00906	3	1427	90	90	HWIIP75	Lung, Pancreas, Colon, Breast/Ovarian
422	836927	(AF027299) protein 4.1-G [Homo sapiens] >sp O4349 O4349  PROTEIN 4.1-G. Length = 1005	gi 2739096	3	1196	84	84	IIDTKY58	Lung, Pancreas
423	837344	SIR [Cowpox virus] >sp O72763 O72763 SIR PROTEIN. Length = 210	gnl PID cl289272	38	658	48	58	HLDA32	Lung, Prostate
424	837789	bikunin [Homo sapiens] >sp O0027 O0027  BIKUNIN. Length = 252	gi 2065529	365	1231	91	91	IIDAIB73	Colon, Breast/Ovarian
425	838549	(AL023828) Y17G7B.14 [Caenorhabditis elegans] >sp E1323274 E1323274 Y17G7B.14 PROTEIN. Length = 364	gnl PID cl323274	2	853	42	55	HDQDW56	Lung, Breast/Ovarian
426	838754			437	1198			HITEQK83	Lung, Pancreas, Breast/Ovarian
427	838768			570	770			IHWBCW80	Lung, Pancreas, Breast/Ovarian
428	839486	fibronectin precursor [Homo sapiens] >gi 4096846 fibronectin [Homo sapiens] {SUB 76-454} >gi 4096848 fibronectin [Homo sapiens] {SUB 1892-2103} >gi 182706 fibronectin [Homo sapiens] {SUB 1921-2040} >gi 182684 fibronectin [Homo sapiens] {SUB 2233-2328} Len	gi 31397	2	493	98	98	HSLGC71	Lung, Breast/Ovarian
429	839561	p34 protein [Rattus sp.] >pir S36779 S36779 ribosome-binding protein p34 - rat >sp Q63742 Q63742 P34 PROTEIN. Length = 307	gnl PID cl1003291	45	1133	86	88	HUVFB27	Lung, Pancreas, Prostate

430	839816	similar to plasmodium merozoite surface antigen precursor (SP:P04933) [Caenorhabditis elegans] >sp Q22585 Q22585 SIMILAR TO PLASMODIUM MEROZITE SURFACE ANTIGEN PRECURSOR. Length = 634	gi 1293808	1	432	46	61	HWADY11	Lung, Breast/Ovarian
431	840068	UMP-CMP kinase [Sus scrofa] >pir JC418 JC418  cytidylate kinase (EC 2.7.4.14) - pig >sp Q29561 KCY_PIG UMP-CMP KINASE (EC 2.7.4.14) (CYTIDYLATE KINASE) (DEOXYCYTIDYLATE KINASE). Length = 196	gn P D d1006692	2	757	97	99	HIE8EH64	Lung, Pancreas, Breast/Ovarian
432	840279	(AF062328) p120 catenin isoform 1AB [Homo sapiens] >sp O60715 O60715 P120 CATENIN ISOFORMS 1AB, 2AB, 3AB AND 4AB. >gi 3152823 (AF062322) p120 catenin isoform 2AB [Homo sapiens] ;SUB 55-962} >gi 3152855 (AF062338) p120 catenin isoform 3AB [Homo sapiens] ;S	gi 3152835	219	1493	93	93	HSRB181	Lung, Pancreas
433	840489	connective tissue growth factor [Homo sapiens] >gi 474934 connective tissue growth factor [Homo sapiens] >pir A40551 A40551 connective tissue growth factor - human >sp P29279 CTGF_HUMAN CONNECTIVE TISSUE GROWTH FACTOR PRECURSOR. >gi 984956 connective tiss	gi 180924	1038	1370	100	100	HOEMS29	Lung, Pancreas

434	840538	glycyl tRNA synthetase [Homo sapiens] >pir A55314 A55314 glycine--tRNA ligase (EC 6.1.1.14) precursor - human >gil 600727 glycyl-tRNA synthetase [Homo sapiens] {SUB 55-739} >gil 3845409 (AC004976) glycyl tRNA synthetase [Homo sapiens] {SUB 348-739} Length =	gnl PID id1006904	1	2298	100	100	HYAAN81	Lung, Pancreas, Prostate, Breast/Ovarian
435	840545			145	1302			HMCCK75	Lung, Pancreas, Colon, Breast/Ovarian
436	840549			1	492			HWHGB33	Lung, Prostate
437	840551	IgG Fc binding protein [Homo sapiens] Length = 5405	gnl PID id1020288	3	1409	93	93	HWLKM77	Lung, Prostate, Colon
438	840557			346	1014			H6EDS19	Prostate, Colon
439	840561	putative [Mus musculus] >pir S15785 S15785 heat-stable antigen-related hypothetical protein HSA-C-mouse >sp Q61692 Q61692 HSA-C GENE CODING FOR HEAT STABLE ANTIGEN. Length = 141	gil 51442	385	495	48	72	HLIBZ07	Lung, Pancreas, Prostate, Colon, Breast/Ovarian
440	840562	(AB008549) type I procollagen C-proteinase enhancer protein [Homo sapiens] >gil 3135316 (AF053336) PCOLCE [Homo sapiens] >sp Q14550 Q14550 TYPE I PROCOLLAGEN C-PROTEINASE ENHANCER PROTEIN. Length = 449	gil 2589011	103	1476	96	96	IISSD165	Lung, Pancreas, Prostate, Colon
441	840564	PQ-rich protein [Homo sapiens] >pir S58222 S58222 PQ-rich protein - human >sp Q15184 Q15184 PQ-RICH PROTEIN. Length = 400	gil 929660	2	688	67	68	HPJDB01	Lung, Pancreas

442	840572	putative [Homo sapiens] >pir[54339]54339 prot-oncogene - human >sp[P35226]BMI1_HUMAN DNA-BINDING PROTEIN BMI-1. Length = 326	gi 291873	3	1172	95	95	HTGAZ34	Prostate, Colon
443	840600			3	119			HYAB130	Prostate, Breast/Ovarian
444	840604	Similarity to Mouse A-RAF proto-oncogene serine/threonine-protein kinase (SW:KRAA_MOUSE):	gnl P1344589	1	1359	82	87	HWLHN58	Lung, Pancreas, Prostate, Breast/Ovarian
445	840608	olfactomedin [Rana eschscholtzii] >pir[A47442]A47442 olfactomedin precursor - bullfrog >sp[Q07081]OLFMRANCA OLFACTOMEDIN PRECURSOR (OLFACTORY MUCUS PROTEIN). Length = 464	gi 294502	200	1549	55	75	HWLFY46	Pancreas, Colon
446	840620			776	1267			HTXGB37	Lung, Prostate
447	840625			138	237			HTXDT74	Lung, Prostate
448	840626	nicotinamide N-methyltransferase [Homo sapiens] >gi 1063610 nicotinamide N-methyltransferase [Homo sapiens] >pir[A54060]A54060 nicotinamide N-methyltransferase (EC 2.1.1.1) - human >sp[P40261]NNMT_HUMAN NICOTINAMIDE N-METHYLTRANSFERASE (EC 2.1.1.1). Length = 196	gi 494989	485	1282	100	100	HULAS90	Lung, Pancreas, Prostate, Colon, Breast/Ovarian
449	840638			16	351			HTTDV02	Prostate, Breast/Ovarian
450	840649	BL34=B cell activation gene [human, Peptide, 196 aa] [Homo sapiens] >pir[J56165]J56165 B cell activation protein BL34 - human Length = 196	bbs 129951	1	651	100	100	HTWCY84	Lung, Prostate
451	840651			2	706			HTTAD76	Pancreas, Prostate

452	840666		2	826		HIT0AF86	Lung, Prostate
453	840681		157	2187		HTA1ER63	Lung, Prostate
454	840682	siah binding protein 1 [Homo sapiens] >sp Q99628 Q99628 SIAH BINDING PROTEIN 1 (FRAGMENT). Length = 541	1	1734	99	HIE9PW64	Lung, Breast/Ovarian
455	840684		3	539		HITCIBT14	Pancreas, Prostate, Breast/Ovarian
456	840697		96	560		HTECA52	Lung, Prostate
457	840698	t-complex-type molecular chaperone TCP1 - human >gi 339211 t-complex 1 protein [Homo sapiens] (SUB 308-365) Length = 556	507	1853	96	HDABW50	Pancreas, Prostate
458	840708		1200	1487		HTEAI173	Lung, Prostate
459	840714	(AF053304) mitotic checkpoint component Bub3 [Homo sapiens] >gi 2921873 (AF047472) spleen mitotic checkpoint BUB3 [Homo sapiens] >gi 3639060 (AF081496) kinetochore protein BUB3 [Homo sapiens] >sp O43684 O43684 SPL1EN MITOTIC CHECKPOINT BUB3. Length = 328	175	1170	100	HTEGU90	Lung, Pancreas, Prostate, Breast/Ovarian
460	840716	(AC005326) asparagine synthetase [Homo sapiens] >sp G3341715 G3341715 ASPARAGINE SYNTHETASE. >gi 703119 asparagine synthetase [Homo sapiens] (SUB 1-83) Length = 561	166	1860	94	HSYAI64	Lung, Prostate, Colon, Breast/Ovarian
461	840721		2	1324		HSUSE92	Lung, Pancreas, Prostate, Colon

462	840735	(AC002425) Gene product with similarity to Rat P8 [Homo sapiens] >gi3202004 (AF069073) P8 protein [Homo sapiens] >gi3202006 (AF069074) P8 protein [Homo sapiens] >sp O60356 O60356 GENE: PRODUCT WITH SIMILARITY TO RAT P8. Length = 82	gi32947054	111	392	64	64	64	HSRDN44	Lung, Pancreas, Prostate, Breast/Ovarian
463	840738			985	1230				HTOJK11	Prostate, Colon
464	840745	52-kD SS-A/Ro autoantigen [Homo sapiens] Length = 475	gi338490	2	694	46	63		HSRGC06	Lung, Prostate, Colon
465	840747	(AC004522) Zn-alpha2-glycoprotein [Homo sapiens] >sp O60386 O60386 ZN-ALPHA2-GLYCOPROTEIN. Length = 334	gi3006228	368	877	95	95		HLDDL02	Lung, Pancreas, Breast/Ovarian
466	840756	(AB005624) rig-analog DNA-binding protein [Sus scrofa] >gi306898 rig-analog protein (putative); putative [Homo sapiens] >gi337416 human homologue of rat insulinoma gene (rig); putative [Homo sapiens] >gi305361 Rig DNA-binding protein (putative); putati	gnlPID d1022359	148	480	97	97		HCHBQ33	Lung, Pancreas, Colon, Breast/Ovarian
467	840776	Notch3 [Homo sapiens] >sp G2668592 G2668592 NOTCH3. Length = 2321	gi2668592	2	364	82	82		HSKJZ22	Lung, Breast/Ovarian
468	840784	aldehyde dehydrogenase 6 [Homo sapiens] >pir A55684 A55684 aldehyde dehydrogenase (NADH) (EC 1.2.1.3) 6 precursor, salivary - human >sp P47895 DHA6_HUMAN ALDEHYDE DEHYDROGENASE 6 (EC 1.2.1.5). Length = 512	gi544482	1	618	94	95		HSKAC75	Lung, Prostate, Colon, Breast/Ovarian



469	840788	P1 gene for c subunit of human mitochondrial ATP synthase gene product [Homo sapiens] >gnl PID d1002920 ATP synthase submit c precursor [Homo sapiens] >pir S34066 S34066 H+-transporting ATP synthase (EC 3.6.1.34) lipid-binding protein P1 precursor, mitoc	gll38430	59	484	85	85	HIFUM32	Lung, Prostate, Colon, Breast/Ovarian
470	840794			162	1646			H01B128	Lung, Pancreas, Prostate, Colon
471	840797	OSF-2p1 [Homo sapiens] >pir S36111 S36111 osteoblast-specific factor 2 - human >sp Q15064 Q15064 OSF-2P1. Length = 779	gnl PID d1003341	2	2371	93	93	HDTIM52	Pancreas, Breast/Ovarian
472	840799			292	510			HWBC148	Lung, Pancreas, Colon, Breast/Ovarian
473	840818	translational initiation factor eIF-2, alpha subunit [Homo sapiens] >sp P05198 P2A_HUMAN EUKARYOTIC TRANSLATION INITIATION FACTOR 2 ALPHA SUBUNIT (EIF-2-ALPHA); (SUB 2-315) Length = 315	gii181995	3	806	100	100	H11BHM68	Lung, Prostate
474	840822	fatty acid synthase [Homo sapiens] >pir G01880 G01880 fatty-acid synthase (EC 2.3.1.85) - human >sp Q16702 Q16702 FATTY ACID SYNTHASE (EC 2.3.1.85) (FATTY-ACID SYNTHASE). Length = 2509	gii915392	1423	2367	93	93	HGBHX28	Lung, Prostate, Colon, Breast/Ovarian
475	840830	diubiquitin [Homo sapiens] >sp Q15205 Q15205 DIUBIQUITIN. Length = 165	gnl PID e321293	1	573	99	99	HFXHP85	Pancreas, Prostate

476	840846	glutathione S-transferase Ha subunit 1 (EC 2.5.1.18) [Homo sapiens] >gil306815 glutathione S-transferase (GST, EC 2.5.1.18) [Homo sapiens] >gil306809 glutathione S-transferase [Homo sapiens] >bbsj76373 glutathione S-transferase Ha1 subunit [EC 2.5.1.18] [	gil306810	144	833	95	95	95	HFVHP57	Prostate, Breast/Ovarian
477	840848	prohibitin [human, Peptide, 272 aa] [Homo sapiens] >pir152690152690 prohibitin - human >sp1P35232 PHB_HUMAN PROHIBITIN. Length = 272	bbsj85638	81	917	93	93	93	IIIIHIM75	Lung, Pancreas, Prostate, Breast/Ovarian
478	840860	NAP [Homo sapiens] >pir1S40510 S40510 nucleosome assembly protein 1-like 1 - human >sp1P55209 NPL1_HUMAN NUCLEOSOME ASSEMBLY PROTEIN 1-LIKE 1 (NAP-1 RELATED PROTEIN). Length = 391	gil189067	92	1309	80	80	80	HDT1JJ39	Lung, Pancreas, Colon, Breast/Ovarian
479	840861	(AL021546) Cytochrome C Oxidase Polypeptide Via-liver precursor (EC 1.9.3.1) [Homo sapiens] >sp1O43714 O43714 CYTOCHROME C OXIDASE POLYPEPTIDE VIA-LIVER PRECURSOR (EC 1.9.3.1) (CYTOCHROME-C OXIDASE) (CYTOCHROME OXIDASE) (CYTOCHROME A(3)) (CYTOCHROME AA(3))	gn1P1D1e1248288	2	520	100	100	100	HFPBO29	Lung, Prostate, Breast/Ovarian
480	840871	DNA polymerase delta small subunit [Homo sapiens] >pir138950 138950 DNA-directed DNA polymerase (EC 2.7.7.7) delta regulatory chain - human >sp1P49005 DPD2_HUMAN DNA POLYMERASE DELTA SMALL SUBUNIT (EC 2.7.7.7). Length = 469	gil1008458	2	628	99	99	99	HSDIX61	Pancreas, Colon, Breast/Ovarian

481	840874	secreted cyclophilin-like protein [Homo sapiens] >gi 181335 cyclophilin B [Homo sapiens] {SUB 9-216} >gi 181250 cyclophilin [Homo sapiens] {SUB 10-216} Length = 216	gi 337999	1	873	94	94	UFTDK64	Lung, Prostate
482	840878	unknown [Homo sapiens] >sp P41271 DAN_HUMAN ZINC FINGER PROTEIN DAN (N03). Length = 180	gn P1D d1006216	227	676	99	100	H2MBT19	Lung, Pancreas, Colon, Breast/Ovarian
483	840880			153	320			HFIXK16	Prostate, Colon, Breast/Ovarian
484	840884	mut'Y homolog [Homo sapiens] >sp Q15830 Q15830 MUTY HOMOLOG. Length = 535	gi 1458228	108	1565	99	99	IIIBCHI18	Lung, Prostate
485	840907			103	366			HETAD58	Pancreas, Prostate
486	840926			76	1347			IIICOMT66	Lung, Pancreas, Prostate
487	840932	ATP synthase beta subunit precursor [Homo sapiens] >pir A33370 A33370 H+-transporting ATP synthase (EC 3.6.1.34) beta chain precursor, mitochondrial - human >sp P06576 ATPB_HUMAN ATP SYNTHASE BETA CHAIN, MITOCHONDRIAL PRECURSOR (EC 3.6.1.34). >gi 28931 bc	gi 179281	2	1675	93	93	IIIFIB389	Lung, Prostate
488	840940	carboxyl reductase [Sus scrofa] >pir JN0703 JN0703 carboxyl reductase (NADPH) (EC 1.1.1.184) - pig >sp Q29529 CBR2_PIG 1.1.1.184 CARBONYL REDUCTASE [NADPH] (EC 1.1.1.184) (NADPH-DEPENDENT CARBONYL REDUCTASE) (LCR). Length = 244	gn P1D d1004479	277	678	61	76	HCHNJ32	Pancreas, Breast/Ovarian

489	840947		2	565		HEGAN45	Lung, Pancreas, Prostate, Breast/Ovarian
490	840959	signal peptidase complex 25 kDa subunit [Canis familiaris] >pir A55012 A55012 signal peptidase 25k chain - dog Length = 226	2	712	99	HEHAD53	Lung, Pancreas, Prostate, Breast/Ovarian
491	840964		177	344		HE8UK92	Prostate, Colon
492	840979	transcription factor-like protein 4 - human Length = 298	11	631	99	HE9HD45	Lung, Pancreas, Prostate, Colon
493	840984	p167 [Homo sapiens] >gnl PID d1010130 The KIAA0139 gene product is related to mouse centrosomin B. [Homo sapiens] >gj 2501783 translation initiation factor 3 large subunit [Homo sapiens] >sp Q14152 Q14152 KIAA0139 PROTEIN. >gj 1399801 p167 [Homo sapiens]	3	3017	91	HE8OC40	Lung, Pancreas, Prostate, Breast/Ovarian
494	840986		1	693		HE8TH60	Pancreas, Prostate, Colon
495	840988		1	465		HE8QQ04	Pancreas, Prostate, Breast/Ovarian
496	840990	(AB010415) dTDP-4-keto-L-rhamnose reductase [Actinobacillus actinomycetemcomitans] >sp O66251 O66251 DTDP-4-KETO-L-RHAMNOSE REDUCTASE. Length = 294	157	1140	32	HE8AM92	Pancreas, Prostate
497	840992	nidogen gene product [Homo sapiens] Length = 1246	3	194	96	HE8BX38	Lung, Prostate, Colon, Breast/Ovarian
498	841009	sin3 associated polypeptide p18 [Homo sapiens] >sp O00422 O00422 SIN3 ASSOCIATED POLYPEPTIDE P18. Length = 153	59	523	92	HE8IGP88	Lung, Pancreas, Prostate, Colon, Breast/Ovarian

499	841012	ribosomal protein L39 [Homo sapiens] >gnl PID d1012131 ribosomal protein L39 [Homo sapiens] >gil 575382 ribosomal protein L39 [Rattus norvegicus] >pir JC4229/R6RT39 ribosomal protein L39 - rat >pir G02654/C102654 ribosomal protein L39 - human Length = 51	gil 1373419	2	217	100	100	HSKXP01	Lung, Pancreas, Breast/Ovarian
500	841016	connexin 43 [Homo sapiens] >gil 29917 gap junction protein (AA 1-382) [Homo sapiens] >pir A35853/A35853 gap junction protein Cx43, cardiac - human >sp P17302/CX41_HUMAN GAP JUNCTION ALPHA-1 PROTEIN (CONNEXIN 43) (CX43) (GAP JUNCTION 43 KD HEART PROTEIN). {	gil 181209	1	810	94	94	HD1D1H3	Lung, Pancreas, Prostate, Colon
501	841017				402	683		HE2AY01	Lung, Prostate
502	841021								
					983	1357		HNAAE75	Lung, Pancreas, Colon, Breast/Ovarian
503	841032	(A B000910) ribosomal protein [Sus scrofa] >gil 684917 L44-like ribosomal protein [Homo sapiens] >gil 1666702 ribosomal protein [Mus musculus] >gil 206732 ribosomal protein L36a [Rattus norvegicus] >pir A29820/R6RT36 ribosomal protein L36a - rat Length = 106	gnl PID d1019960	3	395	100	100	HDQAD36	Lung, Colon
504	841051	small subunit ribonucleotide reductase [Homo sapiens] >pir S25854/S25854 ribonucleoside-diphosphate reductase (EC 1.17.4.1) small chain - human Length = 389	gil 36155	656	880	96	1244	HD1DC65	Lung, Pancreas
505	841064							HDPMF32	Prostate, Colon, Breast/Ovarian

506	841069		81	809		HDPMJ48	Prostate, Breast/Ovarian
507	841072	regulatory protein [Mus musculus] >gil452276 updcf-1 [Mus musculus] >pir4869148691 regulatory protein - mouse >spQ64322NPDI_MOUSE NPDC-1 PROTEIN PRECURSOR. Length = 332	162	1139	91	HDPCF81	Lung, Prostate, Colon, Breast/Ovarian
508	841078		521	706		HDPKD92	Pancreas, Prostate
509	841080	HCNGP gene product [Mus musculus] >pirS26660S26660 HCNGP protein - mouse >spQ02614HCGP_MOUSE TRANSCRIPTIONAL REGULATOR PROTEIN HCNGP. Length = 308	1	936	88	HDPIR07	Prostate, Breast/Ovarian
510	841088	quinone oxidoreductase [Homo sapiens] >gil516534 quinone oxidoreductase2 [Homo sapiens] >pirA32667A32667 NAD(P)H dehydrogenase (quinone) (EC 1.6.99.2) 2 - human Length = 231	320	1096	100	HDPIFX64	Lung, Pancreas, Prostate, Breast/Ovarian
511	841092		1187	1402		HJMBH15	Lung, Colon
512	841095	L protein (AA 1-558) [Homo sapiens] >pirA33616A33616 heterogeneous ribonuclear particle protein L - human Length = 558	2	904	84	H2LAT51	Lung, Pancreas, Colon, Breast/Ovarian
513	841096	(AB013357) 49 kDa zinc finger protein [Mus musculus] Length = 460	510	1907	80	HCFH15	Lung, Pancreas, Breast/Ovarian
514	841102		2	256		HDLAV12	Lung, Pancreas, Prostate, Breast/Ovarian
515	841104	zinc finger protein [Homo sapiens] >pirS33305S33305 finger protein ZNF91 - human Length = 1191	712	2451	54	HDLAB16	Pancreas, Prostate, Breast/Ovarian
516	841108	factor XIII a subunit [Homo sapiens] Length = 732	3	1838	99	HDIHFE82	Lung, Pancreas, Colon

517	841118			320	487		IIDLAE34	Lung, Pancreas, Prostate
518	841119	C11 protein [Homo sapiens] >gi1890300 eukaryotic release factor 1 [Homo sapiens] >gnl PID e118068 C11 protein [Mesocricetus auratus] >pir S50853 S50853 translation releasing factor eRF-1 - human >sp P46055 IERF1_HUMAN EUKARYOTIC PEPTIDE CHAIN RELEASE FACT	gnl PID e118910	123	1367	100	HDPAE95	Lung, Pancreas, Prostate
519	841124	similar to deoxyribose-phosphate aldolase [Caenorhabditis elegans] >sp Q19264 DEOC_CAEEL PUTATIVE DEOXYRIBOSE-PHOSPHATE ALDOLASE (EC 4.1.2.4) (PHOSPHODEOXYRIBOALDOLASE) (DEOXYRIBOALDOLASE). Length = 303	gi 1019952	2	358	62	HDAAB17	Prostate, Colon
520	841137	(AF096285) serine-threonine kinase receptor- associated protein [Mus musculus] >sp G4063383 G4063383 SERINE-THREONINE KINASE RECEPTOR-ASSOCIATED PROTEIN. Length = 351	gi 4063383	3	848	98	IIDAA1P84	Lung, Pancreas, Prostate, Breast/Ovarian
521	841143	fibrillarin [Homo sapiens] >pir A38712 A38712 fibrillarin - human >gi 3399667 (AC005393) FBRL_HUMAN; 34 KD NUCLEOLAR SCLERODERMA ANTIGEN [Homo sapiens] {SUB 4-321} Length = 321	gi 31395	39	1040	100	HCKRMJ87	Pancreas, Prostate, Breast/Ovarian
522	841148			2	1807		HCKRNF38	Lung, Pancreas, Prostate, Colon, Breast/Ovarian
523	841149			324	797		HCKRBS04	Prostate, Breast/Ovarian

524	841151	keratin [Carassius auratus] Length = 455	gij212995	2	1399	45	64	HCRNY54	Lung, Pancreas, Prostate, Colon, Breast/Ovarian
525	841155			103	561			HCHOF85	Prostate, Breast/Ovarian
526	841161	(AB014458) ubiquitin specific protease [Homo sapiens] >sp D1035685 D1035685 UBIQUITIN SPECIFIC PROTEASE. Length = 785	gnl P1D d1035685	3	1199	95	95	HCLCA56	Lung, Prostate
527	841162	set [Homo sapiens] >pir A57984 A45018 template activating factor-1, splice form beta - human Length = 277	gij338039	284	1063	99	100	HCHWR92	Prostate, Colon
528	841163	histone H2A [Mus musculus domesticus] >pir S45110 S45110 histone H2A - mouse >sp Q64426 Q64426 HISTONE H2A (FRAGMENT). Length = 137	gij817939	201	665	100	100	HBMIBF44	Pancreas, Breast/Ovarian
529	841169			21	440			HCHOF83	Lung, Prostate, Colon, Breast/Ovarian
530	841172	CLN3 protein [Homo sapiens] >gnl P1D c283670 CLN3 protein [Homo sapiens] >gij2947055 (AC002425) CLN3 [Homo sapiens] >gij3337387 (AC002544) CLN [Homo sapiens] >gij4102729 (AF015593) CLN3 protein [Homo sapiens] >pir A57219 A57219 Batten disease-related prot	gij1039423	291	740	100	100	HCHAC93	Prostate, Breast/Ovarian
531	841174	zinc finger protein 7 (ZFP7) [Homo sapiens] >pir A34612 A34612 zinc finger protein ZNF7 - human Length = 686	gij340446	3	386	98	98	HCHAW34	Prostate, Breast/Ovarian



532	841179	(AF069517) RNA binding protein DEF-3 [Homo sapiens] >sp O7524 O7524 RNA BINDING PROTEIN DEF-3. Length = 1123	gij3212101	549	1742	85	85	HCHBU86	Lung, Pancreas, Prostate
533	841183	keratin 18 [Homo sapiens] >gij307081 keratin 18 precursor [Homo sapiens] >gij34037 cytokeratin 18 [Homo sapiens] >pir S05481 S05481 keratin 18, type I, cytoskeletal - human >sp P05783 K1CR_HUMAN KERATIN, TYPE I CYTOSKELETAL 18 (CYTOKERATIN 18) (K18) (CK 1	gij386844	1	501	80	92	HCHUE20	Lung, Pancreas, Prostate, Colon, Breast/Ovarian
534	841186	(AJ006215) CMP-N-acetylneuraminic acid synthetase [Mus musculus] >sp O88719 O88719 CMP-N-ACETYLNEURAMINIC ACID SYNTHETASE (EC 2.7.4.3) (ACYLNEURAMINATE CYTIDYLTRANSFERASE) (CMP-SIALATE PYROPHOSPHORYLASE) (CMP-SIALATE SYNTHASE). Length = 432	gn PID e1314953	78	1421	95	97	HCHCG26	Lung, Prostate
535	841204	similar to beta-mannosyltransferase [Caenorhabditis elegans] >sp Q22797 Q22797 SIMILAR TO BETA-MANNOSYLTRANSFERASE. Length = 487	gij470340	1	1407	51	72	HCEEZ02	Lung, Pancreas, Prostate, Colon
536	841206	(AF062484) SDP8 [Mus musculus]		251	1192			HCEEM52	Lung, Prostate
537	841207	>sp O70493 O70493 SDP8. Length = 165	gij3126981	193	585	41	63	IIMTAR23	Prostate, Colon
538	841211	(AC004908) zinc finger protein from gene of uncertain exon structure; similar to Q99676 (PID:g3025333) [Homo sapiens] Length = 430	gij4159888	110	766	47	62	HCEDM42	Prostate, Breast/Ovarian

539	841225	membrane protein [Homo sapiens] >gi 1048989 CD9 antigen [Homo sapiens] >gi 34769 MRP-1 (molality related protein) [Homo sapiens] >hbaj131345 CD9 antigen [human, leukocytes, Peptide, 228 aa] [Homo sapiens] >pirA46123/A40402 CD9 antigen - human >sp P21926	gi 508496	41	865	88	88	HCRB101	Lung, Pancreas, Prostate, Colon
540	841229	P1cdc47 [Homo sapiens] >pir S70583 S70583 CDC47 homolog - human >sp P33993 MCM7_HUMAN DNA REPLICATION LICENSING FACTOR MCM7 (CDC47 HOMOLOG) (P11-MCM3). >gn P1D d1006386 hMCM2 [Homo sapiens] ;SUJ1 177-719; Length = 719	gn P1D d1010177	1	2298	98	98	HCE1D58	Lung, Pancreas, Prostate, Breast/Ovarian
541	841237	NAD(P)H:menadiene oxidoreductase [Homo sapiens] >gi 189292 NAD(P)H:quinone oxidoreductase [Homo sapiens] >pir A41135/A30879 NAD(P)H dehydrogenase (quinone) (EC 1.6.99.2) - human >sp P15559 DHQU_HUMAN NAD(P)H DEHYDROGENASE (QUINONE) 1 (EC 1.6.99.2) (QUINON	gi 189246	141	1028	95	95	HBMTA19	Lung, Pancreas, Prostate, Colon, Breast/Ovarian
542	841241	Thy-1 [Homo sapiens] >pir A02106 TDHU Thy-1 membrane glycoprotein precursor - human Length = 161	gi 339683	128	622	86	87	HBBXFC67	Lung, Pancreas, Prostate, Breast/Ovarian
543	841259	(A1D001528) spermidine aminopropyltransferase [Homo sapiens] >sp O00544 O00544 SPERMIDINE AMINOPROPYLTRANSFERASE. Length = 366	gi 2198557	3	1199	93	93	HCEIC53	Lung, Pancreas, Prostate, Breast/Ovarian

544	841260	FKBP51 [Homo sapiens] >pir C5422 C5422 FK506-binding protein, FKBP51 - human >sp Q13451 FKB5_HUMAN 51 KD FK506- BINDING PROTEIN (FKBP51) (PEPTIDYL- PROLYL CIS-TRANS ISOMERASE) (EC 5.2.1.8) (PIPAE) (ROTAMASE) (34 KD PROGESTERONE RECEPTOR-ASSOCIATED IMMUNO	gij1916641	3	863	88	91	HBGDM14	Lung, Prostate
545	841264			1	618			HBHJU33	Lung, Pancreas, Prostate
546	841275	Lutheran blood group glycoprotein [Homo sapiens] >pir I38000 I38000 Lutheran blood group glycoprotein precursor - human >sp P50895 LU_HUMAN LUTHERAN BLOOD GROUP GLYCOPROTEIN PRECURSOR (B- CAM CELL SURFACE GLYCOPROTEIN) (AUBERGER B ANTIGEN) (F8/G255 ANTIGEN	gij603560	2	1183	89	89	HBGMO35	Prostate, Breast/Ovarian
547	841311	(AF019661) zeta proteasome chain; PSMA5 [Mus musculus] >sp G3805976 G3805976 ZETA PROTEASOME CHAIN. Length = 241	gij3805976	45	836	100	100	HICMY64	Lung, Pancreas, Prostate, Breast/Ovarian
548	841313	neuronal protein 15.6 [unidentified] >sp O0911 O09111 NEURONAL PROTEIN 15.6. Length = 133	gn P1D c306259	11	544	75	82	HBCNM82	Lung, Prostate, Colon, Breast/Ovarian
549	841317	unnamed protein product [unidentified] >gij496609 basic transcription factor 2, 44 kD subunit [Homo sapiens] >sp Q13888 Q13888 BASIC TRANSCRIPTION FACTOR 2, 44 KD SUBUNIT (BASIC TRANSCRIPTION FACTOR 2 P44) (FRAGMENT). >gij173712 basic transcription factor	gn P1D c306259	1155	1553	95	95	HAFSG63	Lung, Prostate
550	841322		gn P1D c306259	200	1402	95	95	HAMGI23	Pancreas, Prostate

551	841331		2	955		HHFJL19	Lung, Breast/Ovarian
552	841332	alpha-2-macroglobulin precursor [Homo sapiens] >pir A94033 MAHU alpha-2-macroglobulin precursor - human >sp P01023 A2M6_HUMAN ALPHA-2-MACROGLOBULIN PRECURSOR (ALPHA-2-M). >gi 825615 alpha2-macroglobulin [Homo sapiens] {SUB 672-746} Length = 1474	2	3856	98	HAPQ079	Lung, Prostate
553	841338		1139	1363		HAIJU58	Pancreas, Prostate
554	841345	yeast methionyl-tRNA synthetase homolog [Homo sapiens] >pir JC5224 JC5224 methionine-tRNA ligase (EC 6.1.1.10) - human >gi 804996 mitoxantrone-resistance associated gene [Homo sapiens] {SUB 423-900} Length = 900	2	2761	94	HAIJAQ46	Lung, Pancreas, Prostate, Breast/Ovarian
555	841349		151	1578		IMWFM73	Lung, Pancreas, Prostate, Breast/Ovarian
556	841355	glucose regulated protein 94 (400 AA) [Mesocricetus auratus] >pir A26258 A26258 endoplasmic - hamster (fragment) >sp P08712 ENPL_MESAU ENDOPLASMIN (94 KD GLUCOSE-REGULATED PROTEIN) (GRP94) (FRAGMENT). Length = 400	2	562	99	HAIJA78	Prostate, Breast/Ovarian
557	841417	arginine-rich nuclear protein [Homo sapiens] >pir A40988 A40988 54K arginine-rich nuclear protein - human >sp Q05519 Q05519 ARGININE- RICH 54 KD NUCLEAR PROTEIN. Length = 484	708	1835	73	HNTC1.10	Lung, Pancreas, Colon, Breast/Ovarian

558	841548		278	613		HIBXDN79	Lung, Breast/Ovarian
559	841632	(AF073298) 4F5rel [Homo sapiens] >gj3641536 (AF073297) 4F5rel [Mus musculus] >sp O75918 O75918.4F5REL. >sp O8889 O8889  4F5REL. Length = 59	49	255	100	HTLGV25	Lung, Breast/Ovarian
560	841662	HYA22 protein - human Length = 338	2	532	78	HLQCP61	Prostate, Colon
561	841771		901	1146		HISYDN46	Lung, Pancreas
562	841827	RTTP [Homo sapiens] >gj3046386 (AF004162) nickel-specific induction protein [Homo sapiens] >sp Q92597 Q92597 RTP, COMPLETE CDS. Length = 394	358	1110	97	HIHFDI26	Pancreas, Prostate
563	841835		1232	1612		IIWLTJ54	Lung, Pancreas, Prostate, Colon, Breast/Ovarian
564	842259		2	691		HHFGF52	Lung, Pancreas, Prostate, Colon
565	842463		600	836		HEIY08	Lung, Pancreas
566	842595	ERp28 [Homo sapiens] >sp P30040 ER29_HUMAN ENDOPLASMIC RETICULUM PROTEIN ERP29 PRECURSOR (ERP31) (ERP28). >sp E1314951 E1314951 ERP28 PRECURSOR. Length = 261	50	916	92	HUIFAB73	Lung, Breast/Ovarian
567	842722		2	1465		HYABB24	Lung, Pancreas, Prostate, Breast/Ovarian
568	842815		780	971		HPMSG47	Pancreas, Colon
569	842818	(AF038954) vacuolar H(+) -ATPase subunit [Homo sapiens] >sp O75348 O75348 VACUOLAR H(+)- ATPASE SUBUNIT. Length = 118	91	477	79	HSNJR03	Lung, Pancreas, Prostate, Breast/Ovarian

570	843251	(AF057297) ornithine decarboxylase antizyme 2 [Homo sapiens] >gi 3766170 (AF057297) ornithine decarboxylase antizyme 2 [Homo sapiens] >sp G3766170 G3766170 ORNITHINE DECARBOXYLASE ANTIZYME 2. >gn P1D1 1020346 product is unknown; seizure-related gene [Mus	gi 3766170	215	745	92	92	HTLIF83	Lung, Breast/Ovarian
571	843422			563	898			HISCW60	Lung, Pancreas, Colon, Breast/Ovarian
572	843784			1307	1864			HCECS78	Lung, Pancreas
573	844017			243	566			HKAIG31	Lung, Colon
574	844138	Epithelin 1 & 2 [Homo sapiens] >gi 3005730 (AF055008) epithelin 1 and 2 [Homo sapiens] >pir C1284 GYHU granulin precursor - human >sp G3005730 G3005730 EPTHELIN 1 AND 2. Length = 593	gi 31193	104	1966	100	100	HDPWW59	Lung, Breast/Ovarian
575	844166	(AF039689) antigen NY-CO-7 [Homo sapiens] >sp O60526 O60526 ANTIGEN NY-CO-7. Length = 303	gi 3170178	1	1020	94	94	HABAIE22	Lung, Pancreas, Prostate, Breast/Ovarian
576	844194			3	707			HE8PH56	Lung, Pancreas, Prostate, Colon, Breast/Ovarian
577	844394			378	635			HHEUP26	Lung, Pancreas, Breast/Ovarian
578	844450	weak similarity to rat TEGT protein (GI:456207) [Caenorhabditis elegans] >sp P91373 P91373 SIMILARITY TO RAT TEGT PROTEIN. Length = 342	gi 1825601	113	1165	61	78	HTXOX92	Lung, Pancreas
579	844534			2	244			HCE3I65	Lung, Pancreas, Breast/Ovarian

580	844535	isocitrate dehydrogenase (NADP+) [Homo sapiens] >pir S57499 S57499 isocitrate dehydrogenase (NADP+) (EC 1.1.1.42) precursor, mitochondrial - human >sp P48735 HDHP_HUMAN ISOCITRATE: DEHYDROGENASE [NADP], MITOCHONDRIAL PRECURSOR (EC 1.1.1.42) (OXALOSUCCINATE	gi 872121	3	1454	96	96	HCWCJ238	Lung, Breast/Ovarian
581	844644	(AJ002308) synaptogyrin 2 [Homo sapiens] >sp O43760 O43760 SYNAPTOGYRIN 2. Length = 224	gn P D e 254905	1	720	91	91	HDH8Q51	Lung, Breast/Ovarian
582	844653	immunoglobulin lambda light chain gene product [Homo sapiens] >pir S25745 S25745 Ig lambda chain - human (fragment) Length = 226	gi 33718	1	732	89	91	HCRQC91	Lung, Pancreas, Colon
583	844659	cathepsin D [Homo sapiens] >gi 29678 precursor polypeptide (AA -20 to 392) [Homo sapiens] >gi 181180 preprocathepsin D [Homo sapiens] >pir A25771 K11H1UD cathepsin D (EC 3.4.23.5) precursor - human >sp P07339 CATD_HUMAN CATHEPSIN D PRECURSOR (EC 3.4.23.5).	gi 179948	21	539	94	94	HLDDQ71	Lung, Breast/Ovarian
584	844796			2	1054			HE6BS09	Colon, Breast/Ovarian
585	844812	(AF040642) contains similarity to transacylases [Caenorhabditis elegans] >sp O44793 O44793 C50D2.7 PROTEIN. Length = 895	gi 2746788	13	1542	33	59	HDFFV13	Lung, Pancreas
586	844894	E25B protein [Mus musculus] >sp O89051 O89051 E25B PROTEIN. Length = 266	gi 3746127	66	1013	96	99	HCLBO47	Lung, Pancreas, Colon

587	845361	phosphoglycerate kinase (EC 2.7.2.3) [Homo sapiens] >gi 387021  phosphoglycerate kinase [Homo sapiens] >gi 35435  coding sequence [Homo sapiens] >pir 159050 KIHUG phosphoglycerate kinase (EC 2.7.2.3) - human length = 417	gi 387020	39	1232	100	100	HIIEUJ91	Pancreas, Colon
588	845620			508	1254			I1W1ICQ46	Lung, Pancreas, Prostate, Breast/Ovarian
589	845639	leukocyte antigen F [Homo sapiens] >gi 3273731 (AF055066) MHC class I HLA-F [Homo sapiens] >pir A60384 A60384 MHC class I histocompatibility antigen HLA-F alpha chain Dew3 precursor - human >sp P30511 HLAF_HUMAN HLA CLASS I HISTOCOMPATIBILITY ANTIGEN, F A	gi 312407	2	814	90	90	HCFNA68	Lung, Pancreas, Colon, Breast/Ovarian
590	845660	Cyr61 [Homo sapiens] >gnl P1D1c311857 Gig1 protein [Homo sapiens] >gi 2196782 (AF003594) growth-factor inducible immediate early gene product CYR61 [Homo sapiens] >gnl P1D1c1249319 hCYR61 protein [Homo sapiens] >sp O00622 CYR6_HUMAN CYR61 PROTEIN PRECURSOR	gi 2130527	1	1365	91	91	HKAJW79	Lung, Pancreas, Prostate, Breast/Ovarian
591	845720			1	261			HKDAF83	Lung, Breast/Ovarian
592	845785			180	509			HSCDT09	Pancreas, Colon, Breast/Ovarian
593	845897			1369	1677			I1ADA1809	Pancreas, Breast/Ovarian



594	845922	beta actin [Ovis aries] >gi 2661136 (AF035774) beta actin [Equus caballus] >gi 3320892 (AF076190) beta-actin [Trichosurus vulpecula] >gi 177968 cytoplasmic beta actin [Homo sapiens] >gnl PID d1021082 (AB004047) beta-actin [Homo sapiens] >gi 28252 beta-act	gi 2182269	1	1239	100	100	100	HW1.QQ65	Lung, Pancreas, Colon
595	846016	(AB005894) ecalectin [Homo sapiens]. >sp O75028 O75028 ECALECTIN. Length = 323	gnl PID d1032501	47	337	97	97	97	HD1.P1T90	Lung, Pancreas
596	846040	0-44 protein [Rattus sp.] >pir 57612 57612 Rat brain 0-44 mRNA, segment 2 - rat >sp P38718 P044_RAT 0-44 PROTEIN. Length = 127	gi 203072	127	585	84	88	88	HLICQ37	Lung, Pancreas, Prostate, Colon, Breast/Ovary/ur
597	846073	protein p68 (AA 1-614) [Homo sapiens] >gi 35220 p68 protein (AA 1-614) [Homo sapiens] >gi 2599360 (AF015812) RNA helicase p68 [Homo sapiens] >pir JC1087 JC1087 RNA helicase, ATP-dependent - human >sp P17844 DDX5_HUMAN PROBABLE RNA-DEPENDENT HELICASE P68	gi 38318	23	1051	91	92	92	HTCWDAW01	Lung, Pancreas
598	846257			286	651				HPWDE09	Lung, Prostate
599	HTXPN06R			65	286				HTXPN06	Lung, Breast/Ovary/ur
600	1121.AQ12R			3	311	71	79	79	1121.AQ12	Pancreas, Colon
601	HWAFU16R	(AB000091) ribosomal protein [Sus scrofa] >gnl PID e1339008 (AL031228) dJ1033B10.4 (40S ribosomal protein S18 (RPS18, KE-3)) [Homo sapiens] >gi 198580 ribosomal protein [Mus musculus] >gi 433447 ribosomal protein S18 [Rattus rattus] >gi 3811382 (AF100956)	gnl PID d1019961	3	320	86	86	86	HWAFU16	Lung, Pancreas, Colon, Breast/Ovary/ur

602	HAEAM91R	(AB005218) L subunit of photosynthetic reaction center complex [Acidiphilium rubrum] >gnl PID d1026488 (AB005219) L subunit of photosynthetic reaction center complex [Acidiphilium angustum] >sp O70105 O70105 L SUBUNIT OF PHOTOSYNTHETIC REACTION CENTER COM	gnl PID d1026481	174	215	66	66	66	HAEAM91	Pancreas, Colon, Breast/Ovarian
603	HOEMT44R	(AB010959) natural killer cell enhancing factor [Cyprinus carpio] Length = 199	gnl PID d1033048	54	431	84	93	93	HOEMT44	Lung, Colon, Breast/Ovarian
604	HE2OW04R	(AF001631) glucose-regulated protein GRP94 [Oryctolagus cuniculus] >sp O18750 ENPL_RABIT1 ENDOPLASMIN (94 KD GLUCOSE-REGULATED PROTEIN) (GRP94) (FRAGMENT). Length = 716	gil2581793	7	297	87	89	89	HE2OW04	Lung, Colon
605	HE2OW04R	(AF012422) ribosomal protein 46 [Drosophila melanogaster] Length = 51	gil2307014	3	143	65	87	87	HE2OW04	Lung, Colon, Breast/Ovarian
606	HAPQP94R	(AF018432) dUTPase [Homo sapiens] >gil144332 deoxyuridine nucleotidohydrolase [Homo sapiens] >gil142118 deoxyuridine triphosphatase [Homo sapiens] >pir G02777 G02777 dUTP pyrophosphatase (EC 3.6.1.23) - human >gil292877 dUTP nucleotidohydrolase [Homo sa	gil2443581	3	320	97	97	97	HAPQP94	Lung, Pancreas, Colon
607	H2CB137R	(AF042107) ribosomal protein S3a [Eimeria tenella] >gil2792508 (AF042107) ribosomal protein S3a [Eimeria tenella] Length = 264	gil2792508	3	182	64	64	64	H2CB137	Colon, Breast/Ovarian
608	HEOPQ13R	(AF042505) cytochrome b [Homo sapiens] >sp G3372377 G3372377 CYTOCHROME b (FRAGMENT). Length = 380	gil3372377	82	216	80	82	82	HEOPQ13	Lung, Colon

609	HCRNC25R	(AF051894) 15 kDa selenoprotein [Homo sapiens] Length = 161	gi 3095111	61	162	100	100	100	HCRNC25	Lung, Pancreas, Colon
610	IIITTF28R	(AF056218) superficial zone protein [Bos taurus] >sp O77765 O77765_SUIP1[FRAGMENT:ZONE] PROTEIN (FRAGMENT). Length = 401	gi 3676501	3	185	73	80		IIITTF28	Pancreas, Colon
611	H2LAY26R	40-kDa keratin protein [Homo sapiens]		24	155				H2LAY26	Pancreas, Colon
612	HAPQA06R	>pir A31370 KRHHU9 keratin 19, type I, cytoskeletal - human Length = 400	gi 386803	2	355	62	62		HAPQA06	Lung, Pancreas, Colon, Breast/Ovarian
613	HAQBM72R	40-kDa keratin protein [Homo sapiens] >pir A31370 KRHHU9 keratin 19, type I, cytoskeletal - human Length = 400	gi 386803	2	145	81	81		HAQBM72	Pancreas, Colon
614	HIBGOK18R	40-kDa keratin protein [Homo sapiens] >pir A31370 KRHHU9 keratin 19, type I, cytoskeletal - human Length = 400	gi 386803	1	429	91	92		HIBGOK18	Lung, Pancreas, Colon, Breast/Ovarian
615	H2MAC07R	acidic ribosomal phosphoprotein (P1) [Homo sapiens] >pir B27125 B6HUP1 acidic ribosomal protein P1 - human Length = 114	gi 190234	111	458	100	100		H2MAC07	Lung, Colon, Breast/Ovarian
616	HTTWKF26R	acidic ribosomal phosphoprotein (P2) [Homo sapiens] >pir C27125 B6HUP2 acidic ribosomal protein P2 - human Length = 115	gi 190236	1	345	95	96		HTTWKF26	Lung, Pancreas, Breast/Ovarian
617	HTAHR89R	ADP,ATP carrier protein T2 - human >sp P12236 ADT3_HUMAN ADP,ATP CARRIER PROTEIN, LIVER ISOFORM T2 (ADP/ATP TRANSLOCASE 3) (ADENINE NUCLEOTIDE TRANSLOCATOR 3) (ANT 3). Length = 298	pir S03894 S03894	13	408	96	96		HTAHR89	Lung, Pancreas

618	HOACE24R	alcohol dehydrogenase [Homo sapiens] >pir A3337 IDEHUE1 aldehyde dehydrogenase (NAD+) (EC 1.2.1.3) 1, cytosolic - human >sp P00352 DHAC_HUMAN ALDEHYDE DEHYDROGENASE, CYTOSOLIC (EC 1.2.1.3) (CLASS 1) (ALHD1) (ALDH-E1). (SUB 2-501) Length = 501	gij178372	3	374	91	92	HOACE24	Pancreas, Colon
619	HOELC27R	aldolase A (EC 4.1.3.13) [Homo sapiens] >gij28597 aldolase A (AA 1-364) [Homo sapiens] >pir S14084 ADHUA fructose-bisphosphate aldolase (EC 4.1.2.13) A - human >sp P04075 ALFA_HUMAN FRUCTOSE- BISPHOSPHATE ALDOLASE A (EC 4.1.2.13) (MUSCLE-TYPE ALDOLASE). (S	gij178351	68	604	100	100	HOELC27	Lung, Pancreas, Breast/Ovarian
620	HWLBS25R	aldolase A [Gallus gallus] >gij409193 aldolase A [Gallus gallus] >bbs 167536 aldolase C=fructose- 1,6-bisphosphate aldolase (EC 4.1.2.13) [chickens, brain, Peptide Partial, 42 aa] [Gallus gallus] >pir 51291 51291 aldolase C - chicken (fragment) Length = 4	gij409191	3	95	90	93	HWLBS25	Lung, Pancreas, Colon, Breast/Ovarian
621	HWLVW62R	alpha-1 type III collagen [Homo sapiens] Length = 345	gij180414	1	213	97	97	HWLVW62	Lung, Colon, Breast/Ovarian
622	HAI SE08R	ALPHA-1-ANTICHYMOTRYPSIN PRECURSOR sp P01011 AACT_H (ACT). >gij4165890 (AF089747) alpha-1- antichymotrypsin precursor [Homo sapiens] (SUB 17-423) >gij177933 alpha-1-antichymotrypsin precursor [Homo sapiens] (SUB 22-423) >gij28332 alpha 1 antichymotrypsin [Homo sapiens] (SU	sp P01011 AACT_H UMAN	3	233	95	97	HAI SE08	Lung, Pancreas

623	HFKHD94R	alpha-2 chain precursor (AA -25 to 1018) (3416 is 2nd base in codon) [Homo sapiens] Length = 1043	gi30076	2	316	97	97	HFKHD94	Pancreas, Breast/Ovarian
624	HCE2M86R	alpha-adaptin (A) (AA 1-977) [Mus musculus] >pir A30111 A30111 alpha-adaptin A - mouse >sp P17426 ADAA_MOUSE ALPHA-ADAPTIN A (CLATHRIN ASSEMBLY PROTEIN COMPLEX 2 ALPHA-A LARGE CHAIN) (100 KD COATED VESICLE PROTEIN A) (PLASMA MEMBRANE ADAPTOR HA2/AP2 ADAPT	gi49878	58	165	75	80	HCE2M86	Lung, Colon, Breast/Ovarian
625	HIOFOA89R	annexin IV (placental anticoagulant protein II) [Homo sapiens] >gnl P1D1011889 annexin IV (carbohydrate-binding protein p33/41) [Homo sapiens] >pir A442077 A42077 annexin.IV - human >sp P09325 ANX4_HUMAN ANNEXIN IV (LIPOCORTIN IV) (ENDONEXIN I) (CHROMOB	gi178699	154	399	94	94	HIOFOA89	Pancreas, Colon, Breast/Ovarian
626	HBWCN69R	beta-1,2-N-acetylglucosaminyltransferase II [Homo sapiens] >pir S66256 S66256 alpha-1,6-mannosyl-glycoprotein beta-1, 2-N-acetylglucosaminyltransferase (EC 2.4.1.143) - human >sp Q10469 GNT2_HUMAN ALPHA-1,6-MANNOSYL-GLYCOPROTEIN BETA-1,2-N-ACETYLGALUCOSAM	gi902745	60	308	88	90	HBWCN69	Pancreas, Colon
627	HLQGB43R	beta-2-microglobulin [Homo sapiens] Length = 119	gi179318	1	78	100	100	HLQGB43	Lung, Pancreas, Colon
628	HCROL58R			3	506			HCROL58	Pancreas, Colon
629	HS2IF12R			83	475			HS2IF12	Pancreas, Colon
630	HWLWA01R			2	538			HWLWA01	Pancreas, Colon

631	HCHMV24R				12	185	HCHMV24	Pancreas, Colon Breast/Ovarian Colon,
632	HCHPT49R				94	303	HCHPT49	Breast/Ovarian
633	HCRMGI2R				2	187	HCRMGI2	Pancreas, Colon
634	HWLWE68R				2	241	HWLWE68	Pancreas, Colon
635	HCHPF59R				24	179	HCHPF59	Pancreas, Breast/Ovarian
636	HS2IA81R				90	351	HS2IA81	Pancreas, Colon
637	HCRCNC17R				11	400	HCRCNC17	Pancreas, Colon
638	HIISDJ39R				14	406	HIISDJ39	Pancreas, Colon
639	HWLEL43R				2	337	HWLEL43	Pancreas, Colon
640	HASCG71R				91	249	HASCG71	Lung, Colon, Breast/Ovarian
641	HOEMO43R				2	184	HOEMO43	Lung, Pancreas, Colon,
642	HIRDJ1T95R	c-erb-B-2 precursor [Homo sapiens] >pir A24571 A24571 protein-tyrosine kinase (EC 2.7.1.112) erbB2 precursor - human >sp P04626 ERB2_HUMAN ERBB-2 RECEPTOR PROTEIN-TYROSINE KINASE PRECURSOR (EC 2.7.1.112) (P185ERBB2) (NEU PROTO-ONCOGENE) (C-ERBB-2). Length	gi 311198		151	231	HIRDJ1T95	Breast/Ovarian Pancreas, Colon
643	HAGIEP27R	C10 protein [Bos taurus] >pir A38464 A38464 33K laminin receptor homolog - bovine Length = 295	gi 163303		3	137	HAGIEP27	Lung, Pancreas, Colon, Breast/Ovarian

644	HSYDGI8R	calmodulin [Homo sapiens] >spQ13942Q13942 CALMODULIN. >pirA56785A56785 calmodulin - pig (fragment) {SUB 80-130} >gil324322 (AF069912) calmodulin [Xiphias gladius] {SUB 80-114} >pirE44101E44101 calmodulin, vasoactive intestinal peptide-binding prote	gil825635	3	422	100	100	100	HSYDGI8	Lung, Pancreas, Colon
645	HLJDZ15R	cathepsin C [Homo sapiens] >gil1947071 prepro dipeptidyl peptidase I [Homo sapiens] >pirS66504S66504 dipeptidyl-peptidase I (EC 3.4.14.1) precursor - human >spIP53634CATC HUMAN DIPEPTIDYL- PEPTIDASE I PRECURSOR (EC 3.4.14.1) (DPP- I) (CATHEPSIN C) (CATHE	gil1006657	3	110	71	77	77	HLJDZ15	Lung, Colon
646	HAHDQ34R	cathepsin D [Homo sapiens] >gil29678 precursor polypeptide (AA -20 to 392) [Homo sapiens] >gil181180 preprocathepsin D [Homo sapiens] >pirA25771KHHUD cathepsin D (EC 3.4.23.5) precursor - human >spIP07339CATD_HUMAN CATHEPSIN D PRECURSOR (EC 3.4.23.5).	gil179948	2	103	100	100	100	HAHDQ34	Lung, Pancreas
647	HTLHI18R	collagen alpha 2(VI) chain precursor, long splice form - human >gil179711 alpha-2 collagen type VI- a [Homo sapiens] {SUB 590-1018} >gil291918 alpha-2 type VI collagen [Homo sapiens] {SUB 315-358} Length = 1018	pirS05378CGHU2A	2	481	89	89	89	HTLHI18	Lung, Pancreas

648	HACAC47R	complement component C3 [Homo sapiens] >pir A94065 C3HU complement C3 precursor - human >sp P01024 CO3_HUMAN COMPLEMENT C3 PRECURSOR [CONTAINS: C3A ANAPHYLATOXIN]. >gil 181130 complement component C3 [Homo sapiens] {SUB 1-24} Length = 1663	gil 179665	1	315	79	80	HACAC47	Lung, Pancreas, Breast/Ovarian
649	III.QFY4IR	complement component C3 [Homo sapiens] >pir A94065 C3HU complement C3 precursor - human >sp P01024 CO3_HUMAN COMPLEMENT C3 PRECURSOR [CONTAINS: C3A ANAPHYLATOXIN]. >gil 181130 complement component C3 [Homo sapiens] {SUB 1-24} Length = 1663	gil 179665	3	377	96	98	III.QFY4I	Lung, Pancreas, Colon, Breast/Ovarian
650	HOFMO83R	cyclin G [Homo sapiens] >gil 1236233 cyclin G1 [Homo sapiens] >gil 1236913 cyclin G1 [Homo sapiens] >pir G02401 G02401 cyclin G1 - human >sp P51959 CG2G_HUMAN G2/MITOTIC- SPECIFIC CYCLIN G1. >gnl PID d1013694 cyclin G [Homo sapiens] {SUB 1-279} >gil 1486361 c	gnl PID d1012016	2	205	87	93	HOFMO83	Pancreas, Breast/Ovarian
651	HFTDR22R	cytochrome b5, hepatic - brown howler monkey (fragment) Length = 87	pir S07959 S07959	136	357	100	100	HFTDR22	Pancreas, Colon, Breast/Ovarian
652	HPJCZ01R	cytochrome c oxidase II [Macaca fascicularis] >pir A27420 A27420 cytochrome-c oxidase (EC 1.9.3.1) chain II - crab-eating macaque mitochondrion (SGCI) >sp P11948 COX2_MACFA CYTOCHROME C OXIDASE POLYPEPTIDE II (EC 1.9.3.1). Length = 227	gil 342255	2	163	44	50	HPJCZ01	Lung, Pancreas, Colon



653	HOEKC39R	cytochrome oxidase I [Homo sapiens] >gi 506829 cytochrome oxidase subunit I [Homo sapiens] >pirA00463 ODHU1 cytochrome-c oxidase (EC 1.9.3.1) chain I - human mitochondrion (SGC1) >sp P00395 COX1_HUMAN CYTOCHROME C OXIDASE POLYPEPTIDE I (EC 1.9.3.1). Leng	gil3006	54	167	91	95	HOEKC39	Lung, Pancreas, Colon
654	HOELI24R	cytochrome oxidase subunit 3 [Homo sapiens] Length = 260	gil2052365	29	166	97	97	HOELI24	Lung, Pancreas, Colon
655	HODEI18R	cytochrome oxidase subunit II [Homo sapiens] >gi 530071 cytochrome oxidase subunit II [Homo sapiens] >gi 530073 cytochrome oxidase subunit II [Homo sapiens] >gi 530077 cytochrome oxidase subunit II [Homo sapiens] >gi 337187 cytochrome oxidase subunit II [	gil530069	1	180	69	72	HODEI18	Lung, Pancreas, Colon
656	HOSNR06R	cytochrome oxidase subunit II [Homo sapiens] >gi 530071 cytochrome oxidase subunit II [Homo sapiens] >gi 530073 cytochrome oxidase subunit II [Homo sapiens] >gi 530077 cytochrome oxidase subunit II [Homo sapiens] >gi 337187 cytochrome oxidase subunit II [	gil530069	269	403	93	95	HOSNR06	Lung, Pancreas
657	HCQDL20R	cytochrome P450 PCN3 [Homo sapiens] >pirA3410 A34101 cytochrome P450 3A5 - human >sp P20815 CP35_HUMAN CYTOCHROME P450 3A5 (EC 1.14.14.1) (CYP11A5) (P450-PCN3). >gi 950342 cytochrome P450 [Homo sapiens] (SUB 1-24) Length = 502	gil181346	39	245	98	98	HCQDL20	Pancreas, Colon

658	H1TOH164R	cyokeratin 15 (AA 1 - 456) [Homo sapiens] >pir S01069 KRHS keratin 15, type I, cytoskeletal - human >sp P19012 K1CO_HUMAN KERATIN, TYPE I CYTOSKELETAL 15 (CYTOKERATIN 15) (K15) (CK 15). Length = 456	gi 34071	149	253	89	89	H1TOH164	Prostatic, Breast/Ovarian
659	HCHBR11R	cyokeratin 8 [Homo sapiens] Length = 483	gi 181400	3	380	55	57	HCHBR11	Lung, Pancreas, Colon, Breast/Ovarian
660	HADBE77R	cytoplasmic chaperonin hTRiCS [Homo sapiens] Length = 201	gi 609308	43	294	80	84	HADBE77	Lung, Pancreas, Colon, Breast/Ovarian
661	HFKHD49R	D-beta-hydroxybutyrate dehydrogenase [Rattus norvegicus] Length = 93	gi 930260	1	210	100	100	HFKHD49	Lung, Colon, Breast/Ovarian
662	HOEMJ59R	decorin [Homo sapiens] >gi 609452 decorin [Homo sapiens] {SUB 1-70} Length = 347	gi 181519	3	128	72	75	HOEMJ59	Lung, Colon
663	H1TYNC43R	elongation factor 1-alpha 1 [Homo sapiens] >gi 927067 elongation factor 1-alpha 1 [Homo sapiens] >pir 59399 59399 oncogene PTL-1 - human >sp Q16577 Q16577 ONCOGENE. Length = 398	gi 927065	2	217	92	94	H1TYNC43	Lung, Pancreas, Colon
664	H6EAQ15R	elongation factor 2 [Homo sapiens] >gi 31108 human elongation factor 2 [Homo sapiens] >pir S18294 EFHU2 translation elongation factor eEF-2 - human >sp P13639 EF2_HUMAN ELONGATION FACTOR 2 (EF-2). >gi 181969 elongation factor 2 [Homo sapiens] {SUB 501-858	gi 31106	2	70	100	100	H6EAQ15	Lung, Pancreas, Breast/Ovarian

665	HCFLM34R	elongation factor Tu [Mus musculus] >sp Q61511 Q61511_EUKARYOTIC TRANSLATION ELONGATION FACTOR 1 ALPHA 1 (EEF-TU GENE ENCODING ELONGATION FACTOR TU, 5' END) (FRAGMENT). Length = 108	48	308	94	95	HCFLM34	Lung, Breast/Ovarian
666	HTTID16R	ENA-78 prepeptide [Homo sapiens] >gi 607031 neutrophil-activating peptide 78 [Homo sapiens] >gi 471243 ENA-78 gene product [Homo sapiens] >pir JC2433 A55010 neutrophil-activating peptide ENA-78 - human >sp P42830 EN78_HUMAN NEUTROPHIL ACTIVATING PROTEIN E	2	331	85	85	HTTID16	Pancreas, Colon
667	HIDPA145R	endoglin [Homo sapiens] >pir S37628 S37628 endoglin - human Length = 625	2	181	65	65	HIDPA145	Pancreas, Colon
668	HKIXL19R	epoxide hydrolase [Homo sapiens] >gi 340390 epoxide hydrolase [Homo sapiens] >gi 34543 epoxide hydrolase (AA 1-455) [Homo sapiens] >gi 458701 epoxide hydrolase [Homo sapiens] >pir A29939 A29939 epoxide hydrolase (EC 3.3.2.3) 1, microsomal - human >sp P070	1	348	100	100	HKIXL19	Lung, Pancreas, Colon
669	H2LAY52R	EWS gene product [Mus musculus] >pir A55726 A55726 RNA-binding protein Ews - mouse >sp Q61545 EWS_MOUSE RNA-BINDING PROTEIN EWS. Length = 655	27	494	100	100	H2LAY52	Lung, Pancreas, Colon, Breast/Ovarian
670	HBJRB09R	FAST kinase [Homo sapiens] >pir J37386 J37386 FAST kinase - human >sp Q14296 Q14296 FAST KINASE. Length = 549	19	324	77	77	HBJRB09	Pancreas, Colon

671	HAPN186R	G9a [Homo sapiens] >pir S30385 S30385 G9a protein - human >sp Q14349 Q14349 G9A PROTEIN CONTAINING ANKYRIN-LIKE REPEATS. Length = 1001	gil287865	3	419	97	97	HAPN186	Lung. Colon
672	HCEVB92R	glutamate dehydrogenase [Homo sapiens] >sp Q14400 Q14400 GLUTAMATE DEHYDROGENASE (FRAGMENT). Length = 258	gil183056	2	217	78	81	HCEVB92	Pancreas, Colon
673	HAPRJ22R	glutamate--ammonia ligase [Homo sapiens] >pir S18455 AJHUQ glutamate--ammonia ligase (EC 6.3.1.2) - human Length = 373	gil31831	168	431	100	100	HAPRJ22	Lung. Pancreas, Prostate, Colon, Breast/Ovarian
674	HCRMZ32R	glutamine:fructose-6-phosphate amidotransferase [Homo sapiens] >pir A45055 A45055 glutamine--fructose-6-phosphate transaminase (isomerizing) (EC 2.6.1.16) - human >sp Q06210 GFAT_HUMAN GLUCOSAMINE--FRUCTOSE-6-PHOSPHATE AMINOTRANSFERASE [ISOMERIZING] (EC 2	gil183082	2	316	91	91	HCRMZ32	Pancreas, Colon, Breast/Ovarian
675	HBVMV42R	guanine nucleotide regulatory protein [Homo sapiens] >gil3041860 (AC004534) guanine nucleotide regulatory protein [Homo sapiens] >pir J38402 J38402 guanine nucleotide regulatory protein - human >sp Q12774 Q12774 GUANINE NUCLEOTIDE REGULATORY PROTEIN. Leng	gil484102	1	363	84	87	HBVMV42	Colon, Breast/Ovarian

676	HAADGI45R	guanine nucleotide-binding protein Gs-alpha-4 [Homo sapiens] >gil31913 alpha-S1 (AA 1-380) [Homo sapiens] >pirC31927/RGHUAI GTP-binding regulatory protein Gs alpha chain (adenylate cyclase-stimulating), splice form 1 - human Length = 380	gil386746	2	439	96	96	IIADGI45	Lung, Pancreas, Colon
677	HTXPNI1R	heat shock-induced protein [Homo sapiens] >pirB45871/B45871 dnaK-type molecular chaperone HSP70-Hom - human >sp P34931/HSP70_HUMAN HEAT SHOCK 70 KD PROTEIN 1-HOM (HSP70-HOM). Length = 641	gil188492	3	413	94	98	HTXPNI1	Lung, Pancreas, Colon
678	HCDBN37R	heterogeneous nuclear ribonucleoprotein C-like protein - human Length = 328	pir A44192 A44192	1	300	96	96	HCDBN37	Colon, Breast/Ovary/Lung, Colon
679	HAIBGC02R	HLA-DR-beta-B [Homo sapiens] Length = 266	gil490048	3	389	89	94	HAIBGC02	Lung, Colon
680	HNTSA70R	HsMem6 [Homo sapiens] >sp Q14566/MCM6_HUMAN DNA REPLICATION LICENSING FACTOR MCM6 (P105MCM). Length = 821	gnl P1D d1013380	3	341	69	72	HNTSA70	Lung, Colon
681	HDTKP24R	hypothetical 18K protein (rRNA) - goldfish mitochondrion (SGC1) Length = 166	pir C1348 C1348	397	492	64	67	HDTKP24	Lung, Pancreas, Colon
682	HODE114R	hypothetical 18K protein (rRNA) - goldfish mitochondrion (SGC1) Length = 166	pir C1348 C1348	164	247	62	68	HODE114	Lung, Pancreas, Colon
683	HOELC42R	(GF-BP-4 [Homo sapiens] >gnl P1D e1227579 insulin-like growth factor binding protein 4 [Homo sapiens] >pir B37252 B37252 insulin-like growth factor-binding protein 4 precursor - human >sp P22692 BP4_HUMAN INSULIN-LIKE GROWTH FACTOR BINDING PROTEIN 4 PREC	gil184816	13	288	83	83	HOELC42	Pancreas, Colon

684	HWAFL44R	immunoglobulin heavy chain [Homo sapiens] >pirD36005D36005 Ig heavy chain V region (M43) - human (SUB 38-156) Length = 156	2	463	83	90	HWAFL44	Lung, Colon
685	HABGF46R	immunoglobulin light chain variable region [Homo sapiens] >gi2970534 (AF049692) immunoglobulin kappa light chain [Homo sapiens] (SUB 3-106) Length = 143	42	446	71	85	HABGF46	Lung, Pancreas, Colon, Breast/Ovarian
686	HOELC15R	insulin-like growth factor-binding protein [Homo sapiens] >gi386791 growth factor-binding protein-3 [Homo sapiens] >gi398164 insulin-like growth factor binding protein 3 [Homo sapiens] >pirA36578 OHU3 insulin-like growth factor-binding protein 3 precu	8	424	96	96	HOELC15	Pancreas, Colon, Breast/Ovarian
687	H2LAR26R	keratin 18 [Homo sapiens] >gi307081 keratin 18 precursor [Homo sapiens] >gi34037 cyto keratin 18 [Homo sapiens] >pirS0548 S0548 keratin 18, type I, cytoskeletal - human >sp P05783 K1CR_HUMAN KERATIN, TYPE I CYTOSKELETAL 18 (CYTOKERATIN 18) (K18) (CK I	72	476	97	98	H2LAR26	Colon, Breast/Ovarian
688	H2LAV85R	Ku (p70/p80) subunit [Homo sapiens] >gi307093 Ku antigen [Homo sapiens] >pirA3505 A32626 Ku antigen 80K chain - human >sp P13010 K1U86_HUMAN ATP-DEPENDENT DNA HELICASE II, 86 KD SUBUNIT (LUPUS KU AUTOANTIGEN PROTEIN P86) (86 KD SUBUNIT OF KU ANTIGEN) (T	67	462	97	98	H2LAV85	Lung, Pancreas
689	HBSDC92R	l-caldesmon II [Homo sapiens] Length = 532	56	337	64	76	HBSDC92	Lung, Breast/Ovarian

690	HUTHN01R	L6 [Homo sapiens] >pir/A42936/A42926 L6 surface protein - human Length = 202	gij186804	87	545	91	91	HUTHN01	Lung, Pancreas, Colon, Breast/Ovarian
691	H2LAW03R	lactate dehydrogenase B [Homo sapiens] >gij34329 lactate dehydrogenase B (AA 1 - 334) [Homo sapiens] >pir/S02795/DEHULH L-lactate dehydrogenase (EC 1.1.1.27) chain H - human >sp P07195 LDHM_HUMAN L-LACTATE DEHYDROGENASE H CHAIN (EC 1.1.1.27) (LDH-B), {SUB	gnijP1Dc223241	111	536	99	100	H2LAW03	Lung, Pancreas
692	HOEMO60R	lactate dehydrogenase-A [Homo sapiens] >gij34313 lactate dehydrogenase-A [Homo sapiens] >pir/A00347/DEHULM L-lactate dehydrogenase (EC 1.1.1.27) chain M - human >sp P00338 LDHM_HUMAN L-LACTATE DEHYDROGENASE M CHAIN (EC 1.1.1.27) (LDH-A), {SUB 2-332} Lengi	gij780261	1	201	59	59	HOEMO60	Pancreas, Breast/Ovarian
693	HKAHJ14R	latent transforming growth factor-beta-binding protein - human Length = 1820	pir/A35494/A55494	1	216	85	86	HKAHJ14	Pancreas, Colon
694	HOHEA39R	lumican [Homo sapiens] Length = 338	gij699377	58	468	97	97	HOHEA39	Pancreas, Breast/Ovarian
695	HOELF72R	M130 antigen [Homo sapiens] >pir 38003 S36077	gij312142	1	432	85	88	HOELF72	Pancreas, Colon
696	HAPNX59R	M130 antigen - human >sp Q07898 Q07898 M130 ANTIGEN PRECURSOR. Length = 1116						HAPNX59	Lung, Colon
697	HBJJS17R	methionine aminopeptidase [Homo sapiens] >gij687243 eIF-2-associated p67 homolog [Homo sapiens] >pir S52112 DPHUM2 methionyl aminopeptidase (EC 3.4.11.18) 2 - human >sp P50579 AMP2_HUMAN METHIONINE AMINOPEPTIDASE 2 (EC 3.4.11.18) (METAP 2) (PEPTIDASE M 2)	gij903982	1	255	100	100	HBJJS17	Lung, Pancreas

698	HATDU61R	midkine [Homo sapiens] >gil188571 retinoic acid inducible factor [Homo sapiens] >gil35087 neurite outgrowth-promoting protein [Homo sapiens] >gnlPIDd1001932 midkine [Homo sapiens] >pirJI10385JI10385 midkine precursor - human >spIP21741IMK_HUMAN MIDKINE	gil182651	1	108	67	67	HATDU61	Pancreas, Colon
699	HCWHT65R	mitochondrial intermediate peptidase precursor [Homo sapiens] >spIQ9797/Q99797 MITOCHONDRIAL INTERMEDIATE PEPTIDASE PRECURSOR (EC 3.4.24.59). Length = 713	gil1763642	1	432	74	77	HCWHT65	Prostate, Colon
700	H2CBN02R	mitochondrial matrix protein [Homo sapiens] >pirA32800/A32800 chaperonin GroEL precursor - human >spPI0809/P60_HUMAN MITOCHONDRIAL MATRIX PROTEIN P1 PRECURSOR (P60 LYMPHOCYTE PROTEIN) (60 KD CHAPERONIN) (HEAT SHOCK PROTEIN 60) (HSP-60) (PROTEIN CPN60) (	gil190127	1	435	99	99	H2CBN02	Pancreas, Colon
701	H2CBV68R	mitochondrial matrix protein [Homo sapiens] >pirA32800/A32800 chaperonin GroEL precursor - human >spPI0809/P60_HUMAN MITOCHONDRIAL MATRIX PROTEIN P1 PRECURSOR (P60 LYMPHOCYTE PROTEIN) (60 KD CHAPERONIN) (HEAT SHOCK PROTEIN 60) (HSP-60) (PROTEIN CPN60) (	gil190127	2	406	100	100	H2CBV68	Colon, Breast/Ovarian



702	H6EDK07R	Mr 110,000 antigen [Homo sapiens] >pir 52703 52703 42K membrane glycoprotein - human >sp Q16186 G100_HUMAN 110 KD CELL MEMBRANE GLYCOPROTEIN. Length = 407	gn P1D1d 011683	1	252	90	90	H6EDK07	Lung, Breast/Ovarian
703	HACAH10R	NADH dehydrogenase subunit 2, ND2 [human, brain, Peptide Mitochondrial Partial Mutant, 67 aa] [Homo sapiens] >sp Q36734 Q36734 NADH DEHYDROGENASE SUBUNIT 2 (FRAGMENT). Length = 67	bbs 75898	1	66	89	96	HACAH10	Lung, Pancreas, Colon
704	HCCMC56R	NADH-UBIQUINONE OXIDOREDUCTASE B18 SUBUNIT (EC 1.6.5.3) (EC 1.6.99.3) (COMPLEX I-B18) (CI-B18) (CELL ADHESION PROTEIN SQM1). Length = 134	sp P17568 NB8M_HUMAN	16	351	83	83	HCCMC56	Lung, Colon, Breast/Ovarian
705	H2CBN54R	NADH-ubiquinone oxidoreductase B22 subunit (C-terminal) [human, placenta, Peptide Mitochondrial Partial, 179 aa] [Homo sapiens] Length = 179	bbs 178894	2	427	99	99	H2CBN54	Pancreas, Colon
706	HMCGL12R	NMB gene product [Homo sapiens] >pir 38065 38065 gene NMB protein - human >sp Q14956 NMB_HUMAN PUTATIVE TRANSMEMBRANE PROTEIN NMB PRECURSOR. Length = 560	gi 666043	96	389	76	80	HMCGL12	Lung, Pancreas
707	HWHPX50R	nucleolar protein [Mus musculus] >pir 52858 52858 nucleolar protein - mouse >sp Q61937 NPM_MOUSE NUCLEOPHOSMIN (NPM) (NUCLEOLAR PHOSPHOPROTEIN B23) (NUMATRIN) (NUCLEOLAR PROTEIN NO38). Length = 292	gi 200011	1	414	87	87	HWHPX50	Lung, Pancreas, Colon, Breast/Ovarian

708	HAPQD84R		115	267		HAPQD84	Lung, Pancreas, Colon, Breast/Ovarian
709	HLIBN66R		1	219		HLIBN66	Lung, Pancreas
710	HE2BD84R	OSF-2p1 [Homo sapiens] >pirS36111 S36111  osteoblast-specific factor 2 - human >spQ15064 Q15064 OSF-2P1. Length = 779	2	394	77	HE2BD84	Pancreas, Colon, Breast/Ovarian
711	HLQFY45R	pancreatitis-associated protein [Homo sapiens] >ejl312807 preprotein [Homo sapiens] >bbs 121222 PAP-H=pancreatitis-associated protein [human, pancreas, Peptide, 175 aa] [Homo sapiens] >gnlPID d1003233 PAP homologous protein [Homo sapiens] >pir/A49616/A49	57	374	60	HLQFY45	Pancreas, Colon
712	HAMQ78R	phosphate carrier isoform A (alternatively spliced, exon IIIA) - human >sp Q00325 MPCP_HUMAN MITOCHONDRIAL PHOSPHATE CARRIER PROTEIN PRECURSOR. Length = 362	2	352	82	HAMQ78	Lung, Colon
713	HODEV64R	poly(A)-binding protein [Homo sapiens] >gil1562511 poly(A)-binding protein [Homo sapiens] >sp P11940 PAB1_HUMAN POLYADENYLATE-BINDING PROTEIN 1 (POLY(A) BINDING PROTEIN 1) (PABP 1). Length = 636	1	492	97	HODEV64	Lung, Pancreas

714	H2CBD48R	precursor polypeptide (AA -21 to 782) [Homo sapiens] >pir A35954 A35954 endoplasmic precursor - human >sp P14625 ENPL_HUMAN ENDOPLASMIN PRECURSOR (94 KD GLUCOSE-REGULATED PROTEIN) (GRP94) (GP96 HOMOLOG) (TUMOR REJECTION ANTIGEN 1). Length = 803	gij37261	2	499	95	97	H2CBD48	Pancreas, Colon
715	HCCMA82R	procarboxypeptidase B [Homo sapiens] >pir A42332 A42332 carboxypeptidase B (EC 3.4.17.2) precursor, pancreatic - human Length = 416	gij189625	3	383	94	94	HCCMA82	Pancreas, Colon
716	H013MK78R	prolactin-stimulating factor, PGL2-stimulating factor, PSF [human, cultured diploid fibroblast cells, Peptide, 282 aa] [Homo sapiens] >pir S50031 S50031 prolactin-stimulating factor - human >sp Q16270 Q16270 PROSTACYCLIN-STIMULATING FACTOR. Length =	blsl161346	3	329	95	95	H013MK78	Lung, Pancreas
717	H2CBD13R	proteasome subunit C9 [Homo sapiens] >pir S15972 SNHUC9 multicatalytic endopeptidase complex (EC 3.4.99.46) chain C9 - human >sp P25789 PRC9_HUMAN PROTEASOME COMPONENT C9 (EC 3.4.99.46) (MACROPAIN SUBUNIT C9) (MULTICATALYTIC ENDOPEPTIDASE COMPLEX SUBUNIT	gnl PID d1001118	156	461	100	100	H2CBD13	Lung, Pancreas, Prostate, Colon, Breast/Ovarian
718	HCFMU61R	protein-tyrosine kinase (EC 2.7.1.112) ZAP-70 - human Length = 619	pir A44266 A44266	1	477	98	98	HCFMU61	Pancreas, Colon

719	HIOSNE94R	proteoglycan core protein [Homo sapiens] >pir A45016 NBHUC8 decorin precursor - human >sp P07585 PGS2_HUMAN BONE PROTEOGLYCAN II PRECURSOR (PG-S2) (DECORIN) (P640). >gil 161226 decorin [Rattus norvegicus] {SUB 204-299} Length = 359	2	466	85	85	HIOSNE94	Lung, Pancreas
720	HCROZ08R	putative precursor (AA 1-304) [Homo sapiens] >gnl PID e224276 uracil-DNA-glycosylase, UNGI [Homo sapiens] >pir S05964 A60472 uracil-DNA glycosylase (EC 3.-.-) precursor - human >gnl PID e1296296 MITOCHONDRIAL LOCALIZATION PEPTIDE [unidentified] {SUB 1-3	3	218	100	100	HCROZ08	Lung, Pancreas, Colon
721	HIIBEF47R	pyruvate dehydrogenase E1-alpha precursor [Homo sapiens] >pir A60225 A60225 pyruvate dehydrogenase (liponamide) (EC 1.2.4.1) alpha chain - bovine (fragment) {SUB 54-74} Length = 414	1	330	88	88	HIIBEF47	Colon, Breast/Ovarian
722	HTXPI31R	pyruvate kinase M2 [Sus scrofa] >sp Q29582 Q29582 PYRUVATE KINASE M2 (EC 2.7.1.40) (PHOSPHOENOLPYRUVATE KINASE) (PHOSPHOENOL TRANSPHOSPHORYLASE) (FRAGMENT). Length = 108	2	286	84	85	HTXPI31	Pancreas, Breast/Ovarian
723	HOEKC30R	rhoC coding region (AA 1-193) [Homo sapiens] >gil 407699 GTPase [Homo sapiens] >pir S01029 TVHURC GTP-binding protein rhoC - human Length = 193	2	151	94	94	HOEKC30	Lung, Pancreas, Breast/Ovarian
724	HOSNR67R	ribosomal protein small subunit [Homo sapiens] Length = 264	1	483	97	98	HOSNR67	Lung, Pancreas

725	H2LAV92R	ribosomal protein [Homo sapiens] >gi 57078 ribosomal protein L38 [Rattus rattus] >pir S15658 R5RT38 ribosomal protein L38 - rat >pir S38385 S38385 ribosomal protein L38 - human >gnl P1 d1026783 (A18007185) ribosomal protein L38 [Homo sapiens] {SUB 34-70}	gi 407423	13	351	72	72	H2LAV92	Lung, Pancreas, Prostate, Colon, Breast/Ovarian
726	H2LAO74R	ribosomal protein L10 [Homo sapiens] >sp D102677 D102677.1 RIBOSOMAL PROTEIN L15 (FRAGMENT). {SUB 16-57} Length = 205	gi 414587	359	502	83	83	H2LAO74	Lung, Pancreas, Colon, Breast/Ovarian
727	HKMMF85R	ribosomal protein L18a [Homo sapiens] >gi 3702270 (AC005796) ribosomal protein L18a [Homo sapiens] >gnl P1 d1029536 (A18007175) ribosomal protein L18a [Homo sapiens] {SUB 111- 176} Length = 176	gi 401845	1	360	96	96	HKMMF85	Lung, Breast/Ovarian
728	HCLBZ27R	ribosomal protein L19 [Homo sapiens] >bbs 127872 ribosomal protein L19 [human, breast cancer cell line, MCF-7, Peptide, 196 aa] [Homo sapiens] >gi 206726 ribosomal protein L19 [Rattus norvegicus] >gnl P1 d18038 ribosomal protein L19 [Rattus norvegicus]	gi 36128	19	273	93	98	HCLBZ27	Lung, Pancreas, Colon
729	H2LAV11R	ribosomal protein L21 [Homo sapiens] >gi 984143 ribosomal protein L21 [Homo sapiens] >pir S55913 S55913 ribosomal protein L21, cytosolic - human >sp D1026774 D1026774 RIBOSOMAL PROTEIN L21 (FRAGMENT). {SUB 124-154} Length = 160	gi 550015	126	530	99	99	H2LAV11	Lung, Pancreas, Colon

730	HBAGP60R	ribosomal protein L27 [Homo sapiens] >gi 3115335 ribosomal protein L27 [Homo sapiens] >gi 57694 ribosomal protein L27 (AA 1-136) [Rattus norvegicus] >gi 62981 ribosomal protein L27 [Gallus gallus] >pir S00401 R5RT27 ribosomal protein L27, cytosolic - ra	gi 388769	161	373	66	70	HBAGP60	Pancreas, Colon
731	HOEMJ56R	ribosomal protein L28 [Homo sapiens] >pir S55915 S55915 ribosomal protein L28 - human Length = 137	gi 550019	3	206	94	94	HOEMJ56	Lung, Colon, Breast/Ovarian
732	HASAF77R	ribosomal protein L31 [Sus scrofa] >gi 36130 ribosomal protein L31 (AA 1-125) [Homo sapiens] >gi 57115 ribosomal protein L31 (AA 1-125) [Rattus norvegicus] >pir S05576 R5HU31 ribosomal protein L31 - human >pir A26417 R5RT31 ribosomal protein L31 - rat >gn	gn P1D1e276436	1	381	82	82	HASAF77	Lung, Prostate, Colon, Breast/Ovarian
733	H2MAC95R	ribosomal protein L37 [Homo sapiens] >bbs 172744 ribosomal protein L37 {C2-C2 zinc-finger-like} (human, HeLa cells, Peptide, 97 aa) [Homo sapiens] >gn P1D1d1005426 ribosomal protein L37 [Homo sapiens] >gi 57121 ribosomal protein L37 [Rattus norvegicus] >	gi 292441	67	411	79	79	H2MAC95	Lung, Colon, Breast/Ovarian
734	I1DPLP40R	ribosomal protein L37 [Homo sapiens] >bbs 172744 ribosomal protein L37 {C2-C2 zinc-finger-like} (human, HeLa cells, Peptide, 97 aa) [Homo sapiens] >gn P1D1d1005426 ribosomal protein L37 [Homo sapiens] >gi 57121 ribosomal protein L37 [Rattus norvegicus] >	gi 292441	1	363	100	100	I1DPLP40	Lung, Pancreas, Breast/Ovarian

735	HOEMK92R	ribosomal protein L37a [Homo sapiens] >gi36134 ribosomal protein L37a [Homo sapiens] >gi57123 ribosomal protein L37a (AA 1 - 92) [Rattus rattus] >gi312414 ribosomal protein L37a [Mus musculus] >pir S05014 R5RT37 ribosomal protein L37a - rat >pir S42109	gi 292439	3	185	96	96	HOEMK92	Lung, Pancreas, Breast/Ovarian
736	HABAD57R	ribosomal protein L4 [Homo sapiens] >pir S39803 S39803 ribosomal protein L4 - human Length = 425	gi 307385	210	431	80	90	HABAD57	Lung, Pancreas
737	HLXNA52R	ribosomal protein L4 [Rattus norvegicus] Length = 421	gnl PID e121603	3	296	86	86	HLXNA52	Lung, Pancreas
738	I1WAFK82R	ribosomal protein L9 [Homo sapiens] >gnl PID d100391 human homologue of rat ribosomal protein L9 [Homo sapiens] Length = 192	gi 710366	139	354	77	78	I1WAFK82	Lung, Colon, Breast/Ovarian
739	H2CBL68R	ribosomal protein S13 [Homo sapiens] >gi488417 ribosomal protein S13 [Homo sapiens] >gnl PID d1014222 ribosomal protein S13 [Homo sapiens] >gi57730 ribosomal protein S13 [Rattus rattus] >pir S34109 S34109 ribosomal protein S13, cytosolic - human >pir A3	gi 307391	3	461	100	100	H2CBL68	Lung, Pancreas
740	HNTNE17R	ribosomal protein S17 [Homo sapiens] >gi 337503 S17 ribosomal protein [Homo sapiens] >pir T0405 R4HU17 ribosomal protein S17, cytosolic - human Length = 135	gi 337501	1	387	100	100	HNTNE17	Lung, Pancreas, Breast/Ovarian
741	HBJLR37R	ribosomal protein S26 [Homo sapiens] Length = 115	gi 296452	2	328	98	100	HBJLR37	Pancreas, Colon, Breast/Ovarian

742	HOSNG20R	ribosomal protein S4X isoform [Homo sapiens] >gi 2791861 (AF041428) ribosomal protein s4 X isoform [Homo sapiens] >gi 200864 ribosomal protein S4 [Mus musculus] >gi 57135 ribosomal protein S4 (AA 1 - 263) [Rattus rattus] >gnl P1D1002335 ribosomal protei	gi 337510	1	357	97	98	HOSNG20	Lung, Pancreas, Colon, Breast/Ovarian
743	HCLBZ30R	ribosomal protein S5 [Mus musculus] Length = 204	gi 1685071	2	244	89	89	HCLBZ30	Lung, Pancreas, Colon, Breast/Ovarian
744	HBGNY11R	ribosomal protein S8 [Homo sapiens] >gi 57139 ribosomal protein S8 (AA 1-208) [Rattus norvegicus] >gi 313298 ribosomal protein S8 [Mus musculus] >pir S01609 R3R78 ribosomal protein S8 - rat >pir S42110 S42110 ribosomal protein S8 - mouse >pir S25022 S2502	gi 36150	2	334	100	100	HBGNY11	Lung, Pancreas, Breast/Ovarian
745	HOEKC80R	S19 ribosomal protein [Homo sapiens] >pir 152692 152692 ribosomal protein S19, cytosolic - human Length = 145	gi 337733	2	376	98	98	HOEKC80	Lung, Pancreas, Colon, Breast/Ovarian
746	HCHBM70R	secretory protein [Homo sapiens] >gi 940946 intestinal trefoil factor [Homo sapiens] >pir A48284 A48284 intestinal trefoil factor 3 precursor - human >sp Q07654 ITF_HUMAN INTESTINAL TREFOIL FACTOR PRECURSOR (HPI1B). Length = 80	gi 402483	1	114	57	57	HCHBM70	Colon, Breast/Ovarian
747	HIFCES53R	semaphorin C [Mus musculus] >pir 148746 148746 semaphorin C - mouse (fragment) >sp Q62179 Q62179 SEMAPHORIN C (SEM C) (FRAGMENT). Length = 782	gi 854328	1	165	80	86	HIFCES53	Colon, Breast/Ovarian



748	HCRQC92R	spermidine/spermine N1-acetyltransferase [Homo sapiens] >gil338336 spermidine/spermine N1-acetyltransferase [Homo sapiens] >sp p21673 ATDA_HUMAN DIAMINE ACETYLTRANSFERASE (EC 2.3.1.57) (SPERMIDINE/SPERMINE N1-ACETYLTRANSFERASE) (SSAT) (PUTRESCINE ACETYL-T	gil338392	3	278	98	98	HCRQC92	Lung, Colon, Breast/Ovarian
749	H/AOAG75R	TARBP-b gene product [Homo sapiens] Length = 277	gil347964	2	418	100	100	H/AOAG75	Lung, Colon
750	H/WAFE36R	TEGT gene product [Homo sapiens] >pir 38334 38334 TEGT (testis enhanced gene transcript) - human Length = 237	gil458545	2	127	100	100	H/WAFE36	Pancreas, Colon
751	HBGOU57R	TIMP gene product [Homo sapiens] >gil182483 prefibroblast collagenase inhibitor [Homo sapiens] >gil189382 collagenase inhibitor [Homo sapiens] >gil37183 precursor [Homo sapiens] >pir A93372 ZYHUEP metalloproteinase tissue inhibitor 1 precursor - human >gi	gil490094	60	314	75	75	HBGOU57	Lung, Pancreas, Breast/Ovarian
752	H/TXPF20R	TIMP gene product [Homo sapiens] >gil182483 prefibroblast collagenase inhibitor [Homo sapiens] >gil189382 collagenase inhibitor [Homo sapiens] >gil37183 precursor [Homo sapiens] >pir A93372 ZYHUEP metalloproteinase tissue inhibitor 1 precursor - human >gi	gil490094	1	549	84	84	H/TXPF20	Lung, Pancreas, Colon, Breast/Ovarian
753	HCRMD09R	transforming growth factor-beta 1 binding protein precursor [Homo sapiens] >pir A35626 A35626 transforming growth factor beta-1-binding protein - human Length = 1394	gil339548	2	460	86	87	HCRMD09	Lung, Pancreas, Colon

754	HAIRB47R	triose-phosphate isomerase [Pan troglodytes] >gi 37247 triosephosphate isomerase [Homo sapiens] >gi 1200507 triosephosphate isomerase [Homo sapiens] >gi 339841 triosephosphate isomerase (EC 5.3.1.1) [Homo sapiens] >pir S29743 ISHUT triose-phosphate isomer	gill76960	2	334	100	100	HAIRB47	Lung, Pancreas, Breast/Ovarian
755	HAIBG36R			6	251			HAIBG36	Lung, Breast/Ovarian
756	HADBF86R			3	158			HADBF86	Lung, Colon
757	HADDP09R			2	97			HADDP09	Lung, Pancreas, Colon, Breast/Ovarian
758	HAGCY06R			2	58			HAGCY06	Pancreas, Breast/Ovarian
759	HAGDI75R			1	66			HAGDI75	Colon, Breast/Ovarian
760	HAHBD47R			118	429			HAHBD47	Lung, Pancreas
761	HAHCR61R			165	422			HAHCR61	Pancreas, Colon
762	HAJAU22R			101	202			HAJAU22	Pancreas, Colon
763	HAMGB62R			212	370			HAMGB62	Lung, Pancreas, Colon, Breast/Ovarian
764	HANGC52R			3	98			HANGC52	Lung, Pancreas, Colon
765	HAICF30R			2	94			HAICF30	Lung, Colon
766	HAPPV45R			216	536			HAPPV45	Lung, Pancreas
767	HAPQK19R			200	415			HAPQK19	Lung, Pancreas
768	HAPRL82R			3	233			HAPRL82	Lung, Pancreas
769	HAQBT45R			40	255			HAQBT45	Lung, Colon
770	HAUAL56R			127	315			HAUAL56	Pancreas, Breast/Ovarian

771	HAUBR22R	2	67	HAUBR22	Pancreas, Colon, Breast/Ovarian
772	HBAFN19R	3	257	HBAFN19	Lung, Colon, Breast/Ovarian
773	H3GOK25R	274	528	H3GOK25	Pancreas, Colon
774	H3GRA76R	2	88	H3GRA76	Pancreas, Colon
775	H3GRB47R	1	111	H3GRB47	Lung, Pancreas, Colon
776	HBJAS24R	1	66	HBJAS24	Breast/Ovarian
777	HBJKI05R	207	362	HBJKI05	Colon, Breast/Ovarian
778	H3KEC86R	254	409	H3KEC86	Pancreas, Colon
779	H3LGD42R	3	341	H3LGD42	Pancreas, Colon Lung, Pancreas, Colon
780	H3PAF10R	3	65	H3PAF10	Breast/Ovarian
781	HCDBU02R	65	184	HCDBU02	Lung, Pancreas
782	HCDBU04R	64	348	HCDBU04	Pancreas, Colon Lung, Pancreas, Colon
783	HCDDT61R	2	121	HCDDT61	Pancreas, Colon
784	HCEGY65R	2	79	HCEGY65	Pancreas, Colon
785	HCHAK80R	1	513	HCHAK80	Colon, Breast/Ovarian
786	HCHMW79R	73	432	HCHMW79	Pancreas, Breast/Ovarian
787	HCHOB92R	93	350	HCHOB92	Colon, Breast/Ovarian
788	HCLBO01R	45	149	HCLBO01	Lung, Colon
789	HCQAN60R	3	122	HCQAN60	Pancreas, Colon
790	HCRAK70R	3	293	HCRAK70	Colon, Breast/Ovarian
791	HCRPC63R	1	129	HCRPC63	Pancreas, Colon
792	HCUDC51R	2	265	HCUDC51	Lung, Colon

793	HDPFI40R	139	453	HDPFI40	Lung, Pancreas, Breast/Ovarian
794	HDPLP23R	1	141	HDPLP23	Pancreas, Colon, Breast/Ovarian
795	IIDPRZ54R	1	165	IIDPRZ54	Colon, Breast/Ovarian
796	HE9DP46R	2	166	HE9DP46	Lung, Pancreas, Colon
797	HEGAR19R	361	534	HEGAR19	Lung, Colon
798	HFAUO64R	27	137	HFAUO64	Colon, Breast/Ovarian
799	HFIAL90R	186	308	HFIAL90	Lung, Colon
800	HHBEQ12R	218	514	HHBEQ12	Lung, Pancreas
801	HHEUL94R	2	127	HHEUL94	Lung, Pancreas, Colon
802	HISCF76R	16	153	HISCF76	Pancreas, Colon
803	HJMAU64R	1	207	HJMAU64	Lung, Colon
804	IUPCI25R	275	508	IUPCI25	Lung, Pancreas, Colon
805	HKBAC48R	369	542	HKBAC48	Lung, Pancreas, Colon, Breast/Ovarian
806	HKBAD57R	165	341	HKBAD57	Lung, Pancreas
807	HKDBA91R	3	332	HKDBA91	Pancreas, Colon
808	HKGDB80R	3	224	HKGDB80	Lung, Colon
809	HLDNC95R	289	537	HLDNC95	Lung, Pancreas, Prostate, Colon
810	HMSNI52R	2	271	HMSNI52	Lung, Pancreas
811	HODAY16R	134	298	HODAY16	Colon, Breast/Ovarian
812	HODEA57R	289	471	HODEA57	Lung, Pancreas
813	HOEMO27R	1	60	HOEMO27	Colon, Breast/Ovarian

814	HOEMO62R	2	73	HOEMO62	Pancreas, Breast/Ovarian
815	HOEMS18R	1	102	HOEMS18	Lung, Pancreas, Colon,
816	HOENU53R	115	267	HOENU53	Lung, Colon
817	HOGAP33R	1	498	HOGAP33	Pancreas, Prostate, Breast/Ovarian
818	HOSMV34R	124	327	HOSMV34	Lung, Pancreas, Breast/Ovarian
819	HOSNF25R	405	587	HOSNF25	Pancreas, Colon
820	HOUHO32R	230	391	HOUHO32	Lung, Colon
821	HPIAC23R	2	286	HPIAC23	Lung, Breast/Ovarian
822	HRAAD31R	115	414	HRAAD31	Lung, Colon
823	HRACR12R	2	100	HRACR12	Pancreas, Colon
824	HRADJ57R	2	142	HRADJ57	Lung, Colon
825	HROAX48R	184	285	HROAX48	Pancreas, Colon
826	HTAHR87R	369	491	HTAHR87	Lung, Pancreas
827	HTTIO45R	1	288	HTTIO45	Colon, Breast/Ovarian
828	HTWDH05R	1	420	HTWDH05	Lung, Pancreas, Colon,
829	HUFDS13R	51	152	HUFDS13	Breast/Ovarian
830	HUSZE86R	2	340	HUSZE86	Pancreas, Colon
831	HUTHF75R	161	418	HUTHF75	Pancreas, Colon
832	HWAFW07R	3	170	HWAFW07	Lung, Pancreas, Breast/Ovarian
833	HWLIB82R	209	403	HWLIB82	Colon
834	HWLLX91R	147	302	HWLLX91	Pancreas, Colon
835	HWLMZ54R	1	120	HWLMZ54	Lung, Colon Pancreas, Colon

836	HMIA178R		173	319		HMIA178	Pancreas, Colon, Breast/Ovarian
837	HGGFJ39R	unknown product specific to adipose tissue [Homo sapiens] >sp Q15847 Q15847 HYPOTHETICAL 7.9 KD PROTEIN. Length = 76	gnl P D d 100882	153	100	HGGFJ39	Pancreas, Colon
838	HAMHH32R		1	123		HAMHH32	Lung, Colon
839	HAQBQ95R		104	205		HAQBQ95	Colon, Breast/Ovarian
840	HAGHY58R	URF 1 (NADH dehydrogenase subunit) [Homo sapiens] >gi 337189 protein 1 [Homo sapiens] >pir A00407 DNHUN1 NADH dehydrogenase (ubiquinone) (EC 1.6.5.3) chain 1 - human mitochondrion (SGC1) >sp P03886 NUIIM_HUMAN NADH-UBIQUINONE OXIDOREDUCTASE CHAIN 1 (EC 1.6	gi 13004	411	95	HAGHY58	Lung, Colon
841	HOSNE37R	URF 2 (NADH dehydrogenase subunit) [Homo sapiens] >gi 2052363 protein 2 [Homo sapiens] >gi 2582057 (AF014882) NADH dehydrogenase subunit 2 [Homo sapiens] >gi 2582061 (AF014884) NADH dehydrogenase subunit 2 [Homo sapiens] >gi 2582063 (AF014885) NADH dehydr	gi 578710	231	59	HOSNE37	Lung, Pancreas, Colon
842	HWAFE41R	VDUP1=1,25-dihydroxyvitamin D-3 up-regulated [human, HL-60 promyelocytic leukemia cells, Peptide, 39] aa [Homo sapiens] Length = 391	bbs 155932	508	84	HWAFE41	Pancreas, Colon

The first column of Table 1 shows the "SEQ ID NO:" for each of the 842 cancer antigen polynucleotide sequences of the invention.

The second column in Table 1, provides a unique "Sequence/Contig ID" identification for each cancer associated sequence. The third column in Table 1, "Gene Name," provides a putative identification of the gene based on the sequence similarity of its translation product to an amino acid sequence found in a publicly accessible gene database, such as GenBank (NCBI). The great majority of the cDNA sequences reported in Table 1 are unrelated to any sequences previously described in the literature. The fourth column, in Table 1, "Overlap," provides the database accession no. for the database sequence having similarity. The fifth and sixth columns in Table 1 provide the location (nucleotide position nos. within the contig), "Start" and "End", in the polynucleotide sequence "SEQ ID NO:X" that delineate the preferred ORF shown in the sequence listing as SEQ ID NO:Y. In one embodiment, the invention provides a protein comprising, or alternatively consisting of, a polypeptide encoded by the portion of SEQ ID NO:X delineated by the nucleotide position nos. "Start" and "End". Also provided are polynucleotides encoding such proteins and the complementary strand thereto. The seventh and eighth columns provide the "% Identity" (percent identity) and "% Similarity" (percent similarity) observed between the aligned sequence segments of the translation product of SEQ ID NO:X and the database sequence.

The ninth column of Table 1 provides a unique "Clone ID" for a clone related to each contig sequence. This clone ID references the cDNA clone which contains at least the 5' most sequence of the assembled contig and at least a portion of SEQ ID NO:X was determined by directly sequencing the referenced clone. The reference clone may have more sequence than described in the sequence listing or the clone may have less. In the vast majority of cases, however, the clone is believed to encode a full-length polypeptide. In the case where a clone is not full-length, a full-length cDNA can be obtained by methods described elsewhere herein.

The tenth column of Table 1, "Tissue," provides the tissue source where each unique SEQ ID NO:X was found to be predominantly expressed.

Table 3 indicates public ESTs, of which at least one, two, three, four, five, ten, or more of any one or more of these public ESTs are optionally excluded from the invention.

SEQ ID NO:X (where X may be any of the polynucleotide sequences disclosed in the sequence listing as SEQ ID NO:1 through SEQ ID NO:842) and the translated SEQ ID NO:Y

(where Y may be any of the polypeptide sequences disclosed in the sequence listing as SEQ ID NO:843 through SEQ ID NO:1684) are sufficiently accurate and otherwise suitable for a variety of uses well known in the art and described further below. For instance, SEQ ID NO:X has uses including, but not limited to, in designing nucleic acid hybridization probes that will detect nucleic acid sequences contained in SEQ ID NO:X or the related cDNA clone contained in a library deposited with the ATCC. These probes will also hybridize to nucleic acid molecules in biological samples, thereby enabling immediate applications in chromosome mapping, linkage analysis, tissue identification and/or typing, and a variety of forensic and diagnostic methods of the invention. Similarly, polypeptides identified from SEQ ID NO:Y have uses that include, but are not limited to, generating antibodies which bind specifically to the cancer antigen polypeptides, or fragments thereof, and/or to the cancer antigen polypeptides encoded by the cDNA clones identified in Table 1.

Nevertheless, DNA sequences generated by sequencing reactions can contain sequencing errors. The errors exist as misidentified nucleotides, or as insertions or deletions of nucleotides in the generated DNA sequence. The erroneously inserted or deleted nucleotides cause frame shifts in the reading frames of the predicted amino acid sequence. In these cases, the predicted amino acid sequence diverges from the actual amino acid sequence, even though the generated DNA sequence may be greater than 99.9% identical to the actual DNA sequence (for example, one base insertion or deletion in an open reading frame of over 1000 bases).

Accordingly, for those applications requiring precision in the nucleotide sequence or the amino acid sequence, the present invention provides not only the generated nucleotide sequence identified as SEQ ID NO:X, the predicted translated amino acid sequence identified as SEQ ID NO:Y, but also a sample of plasmid DNA containing the related cDNA clone (deposited with the ATCC, as set forth in Table 1). The nucleotide sequence of each deposited clone can readily be determined by sequencing the deposited clone in accordance with known methods. Further, techniques known in the art can be used to verify the nucleotide sequences of SEQ ID NO:X.

The predicted amino acid sequence can then be verified from such deposits. Moreover, the amino acid sequence of the protein encoded by a particular clone can also be directly determined by peptide sequencing or by expressing the protein in a suitable host cell containing the deposited human cDNA, collecting the protein, and determining its sequence.



The present invention also relates to vectors or plasmids which include such DNA sequences, as well as the use of the DNA sequences. The material deposited with the ATCC on:

5    **Table 2**

ATCC Deposits	Deposit Date	ATCC Designation Number
LP01, LP02, LP03, LP04, LP05, LP06, LP07, LP08, LP09, LP10, LP11,	May-20-97	209059, 209060, 209061, 209062, 209063, 209064, 209065, 209066, 209067, 209068, 209069
LP12	Jan-12-98	209579
LP13	Jan-12-98	209578
LP14	Jul-16-98	203067
LP15	Jul-16-98	203068
LP16	Feb-1-99	203609
LP17	Feb-1-99	203610
LP20	Nov-17-98	203485
LP21	Jun-18-99	PTA-252
LP22	Jun-18-99	PTA-253
LP23	Dec-22-99	PTA-1081

each is a mixture of cDNA clones derived from a variety of human tissue and cloned in either a plasmid vector or a phage vector, as shown in Table 5. These deposits are referred to as "the deposits" herein. The tissues from which the clones were derived are listed in Table 5, and the vector in which the cDNA is contained is also indicated in Table 5. The deposited material includes the cDNA clones which were partially sequenced and are related to the SEQ ID NO:X described in Table 1 (column 9). Thus, a clone which is isolatable from the ATCC Deposits by use of a sequence listed as SEQ ID NO:X may include the entire coding region of a human gene or in other cases such clone may include a substantial portion of the coding region of a human gene. Although the sequence listing lists only a portion of the DNA sequence in a clone included in the ATCC Deposits, it is well within the ability of one skilled in the art to complete the sequence of the DNA included in a clone isolatable from the

ATCC Deposits by use of a sequence (or portion thereof) listed in Table 1 by procedures hereinafter further described, and others apparent to those skilled in the art.

Also provided in Table 5 is the name of the vector which contains the cDNA clone. Each vector is routinely used in the art. The following additional information is provided for  
5 convenience.

Vectors Lambda Zap (U.S. Patent Nos. 5,128,256 and 5,286,636), Uni-Zap XR (U.S. Patent Nos. 5,128, 256 and 5,286,636), Zap Express (U.S. Patent Nos. 5,128,256 and 5,286,636), pBluescript (pBS) (Short, J. M. et al., *Nucleic Acids Res.* 16:7583-7600 (1988); Alting-Mees, M. A. and Short, J. M., *Nucleic Acids Res.* 17:9494 (1989)) and pBK (Alting-  
10 Mees, M. A. et al., *Strategies* 5:58-61 (1992)) are commercially available from Stratagene Cloning Systems, Inc., 11011 N. Torrey Pines Road, La Jolla, CA, 92037. pBS contains an ampicillin resistance gene and pBK contains a neomycin resistance gene. Phagemid pBS may be excised from the Lambda Zap and Uni-Zap XR vectors, and phagemid pBK may be excised from the Zap Express vector. Both phagemids may be transformed into *E. coli* strain  
15 XL-1 Blue, also available from Stratagene.

Vectors pSport1, pCMVSport 1.0, pCMVSport 2.0 and pCMVSport 3.0, were obtained from Life Technologies, Inc., P. O. Box 6009, Gaithersburg, MD 20897. All Sport vectors contain an ampicillin resistance gene and may be transformed into *E. coli* strain DH10B, also available from Life Technologies. See, for instance, Gruber, C. E., et al., *Focus*  
20 15:59 (1993). Vector lacmid BA (Bento Soares, Columbia University, New York, NY) contains an ampicillin resistance gene and can be transformed into *E. coli* strain XL-1 Blue. Vector pCR<sup>®</sup>2.1, which is available from Invitrogen, 1600 Faraday Avenue, Carlsbad, CA 92008, contains an ampicillin resistance gene and may be transformed into *E. coli* strain DH10B, available from Life Technologies. See, for instance, Clark, J. M., *Nuc. Acids Res.*  
25 16:9677-9686 (1988) and Mead, D. et al., *Bio/Technology* 9: (1991).

The present invention also relates to the genes corresponding to SEQ ID NO:X, SEQ ID NO:Y, and/or the cDNA contained in a deposited cDNA clone. The corresponding gene can be isolated in accordance with known methods using the sequence information disclosed herein. Such methods include, but are not limited to, preparing probes or primers from the  
30 disclosed sequence and identifying or amplifying the corresponding gene from appropriate sources of genomic material.

Also provided in the present invention are allelic variants, orthologs, and/or species homologs. Procedures known in the art can be used to obtain full-length genes, allelic variants, splice variants, full-length coding portions, orthologs, and/or species homologs of genes corresponding to SEQ ID NO:X, SEQ ID NO:Y, and/or the cDNA contained in the related cDNA clone in the deposit, using information from the sequences disclosed herein or the clones deposited with the ATCC. For example, allelic variants and/or species homologs may be isolated and identified by making suitable probes or primers from the sequences provided herein and screening a suitable nucleic acid source for allelic variants and/or the desired homologue.

10 The present invention provides a polynucleotide comprising, or alternatively consisting of, the nucleic acid sequence of SEQ ID NO:X, and/or the related cDNA clone (See, e.g., columns 1 and 9 of Table 1). The present invention also provides a polypeptide comprising, or alternatively, consisting of, the polypeptide sequence of SEQ ID NO:Y, a polypeptide encoded by SEQ ID NO:X, and/or a polypeptide encoded by the cDNA in the related cDNA clone contained in a deposited library. Polynucleotides encoding a polypeptide comprising, or alternatively consisting of, the polypeptide sequence of SEQ ID NO:Y, a polypeptide encoded by SEQ ID NO:X, and/or a polypeptide encoded by the the dDNA in the related cDNA clone contained in a deposited library, are also encompassed by the invention. The present invention further encompasses a polynucleotide comprising, or alternatively consisting of, the complement of the nucleic acid sequence of SEQ ID NO:X, and/or the complement of the coding strand of the related cDNA clone contained in a deposited library.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence would unduly burden the disclosure of this application. Accordingly, for each "Contig Id" listed in the first column of Table 3, preferably excluded are one or more polynucleotides comprising a nucleotide sequence described in the second column of Table 3 by the general formula of a-b, each of which are uniquely defined for the SEQ ID NO:X corresponding to that Contig Id in Table 1. Additionally, specific embodiments are directed to polynucleotide sequences excluding at least one, two, three, four, five, ten, or more of the specific polynucleotide sequences referenced by the Genbank Accession No. for each Contig Id which may be

included in column 3 of Table 3. In no way is this listing meant to encompass all of the sequences which may be excluded by the general formula, it is just a representative example.

Table 3.

Sequence/ Contig ID	General formula	Genbank Accession No.
507291	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 542 of SEQ ID NO:1, b is an integer of 15 to 556, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:1, and where b is greater than or equal to a + 14.	
508000	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2648 of SEQ ID NO:2, b is an integer of 15 to 2662, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:2, and where b is greater than or equal to a + 14.	T40333, T41194, T66286, T66339, T73997, T86453, T87207, R17614, R19835, R43336, R45934, R48920, R53521, R43336, R45934, R61813, R75928, R75937, H30115, H42959, H39114, H43825, AA028010, AA028107, AA028148, AA031964, AA032046, AA035668, AA190570, AA233781, AA461489, AA460726, AA460898
518325	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 324 of SEQ ID NO:3, b is an integer of 15 to 338, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:3, and where b is greater than or equal to a + 14.	
523111	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 799 of SEQ ID NO:4, b is an integer of 15 to 813, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:4, and where b is greater than or equal to a + 14.	
526869	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 887 of SEQ ID NO:5, b is an integer of 15 to 901, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:5, and where b is greater than or equal to a + 14.	AA459771
532211	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 717 of SEQ ID NO:6, b is an integer of 15 to 731, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:6, and where b is greater than or equal to a + 14.	H30209, H92182, W95693, W95692, AA196967
532247	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b,	R14583, R93797, H52942, H75493, H78857, W17094, W38705, W81551, W90159, N90874, AA010244,

	where a is any integer between 1 to 2760 of SEQ ID NO:7, b is an integer of 15 to 2774, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:7, and where b is greater than or equal to a + 14.	AA029093, AA126501, AA147066
537932	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2599 of SEQ ID NO:8, b is an integer of 15 to 2613, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:8, and where b is greater than or equal to a + 14.	T91131, T84801, T85952, R59198, R59256, H43456, H59480, H79111, N26560, N35676, N64506, N66078, N76033, N78705, W07594, W70111, W70169, N90844, AA026910, AA026911, AA057689, AA079631, AA079805, AA131257, AA136081, AA165115, AA210764, AA211886, AA232838, AA262352
540117	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1087 of SEQ ID NO:9, b is an integer of 15 to 1101, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:9, and where b is greater than or equal to a + 14.	T49371, T49372, T49850, T61568, T64892, N39534, W57682, AA031859
547710	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1359 of SEQ ID NO:10, b is an integer of 15 to 1373, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:10, and where b is greater than or equal to a + 14.	R11154, R11155, R61204, R61205, R82674, H06105, R88575, R88638, H89977, H97031, N20224, W01143, W39387, W90318, W90788, AA001027, AA045864, AA045839, AA070190, AA070357, AA070481, AA074270, AA099007, AA099084, AA100370, AA112324, AA113319, AA158425, AA161510, AA171909, AA172133, AA173087, AA181768, AA188815, AA188874, AA190370, AA226831, AA252143
551747	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 3790 of SEQ ID NO:11, b is an integer of 15 to 3804, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:11, and where b is greater than or equal to a + 14.	
552799	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2143 of SEQ ID NO:12, b is an integer of 15 to 2157, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:12, and where b is greater than or equal to a + 14.	
553243	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1103 of SEQ ID NO:13, b is an integer of 15 to 1117, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:13, and where b is	H63183, W61352, AA151059

	greater than or equal to $a + 14$ .	
553368	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 871 of SEQ ID NO:14, b is an integer of 15 to 885, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:14, and where b is greater than or equal to $a + 14$ .	
554349	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1010 of SEQ ID NO:15, b is an integer of 15 to 1024, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:15, and where b is greater than or equal to $a + 14$ .	
558491	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 531 of SEQ ID NO:16, b is an integer of 15 to 545, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:16, and where b is greater than or equal to $a + 14$ .	
558983	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 609 of SEQ ID NO:17, b is an integer of 15 to 623, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:17, and where b is greater than or equal to $a + 14$ .	
572943	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 545 of SEQ ID NO:18, b is an integer of 15 to 559, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:18, and where b is greater than or equal to $a + 14$ .	
585892	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1341 of SEQ ID NO:19, b is an integer of 15 to 1355, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:19, and where b is greater than or equal to $a + 14$ .	
589390	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1266 of SEQ ID NO:20, b is an integer of 15 to 1280, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:20, and where b is greater than or equal to $a + 14$ .	T47628, T49403, T49829, T49830, T50800, T50963, T51976, T55846, T55860, T55896, T55911, T58744, T58811, T58891, T59252, T59279, T59293, T59615, T59690, T59727, T59826, T60434, T60514, T60584, T61357, T40352, T62559, T62688, T62839, T63122, T64603, T64640,

		T67682, T67756, T68181, T68439, T68506, T68606, T68718, T68783, T68839, T68849, T68976, T69049, T71223, T71347, T71509, T71853, T71858, T71938, T72197, T72264, T72414, T72471, T72923, T73204, T73259, T73283, T73446, T73607, T73621, T73645, T73713, T73744, T73772, T73796, T74114, T74545, T74599, T87829, T90307, T90394, T91481, T92437, T92617, T81767, T82080, R27059, R27060, R31693, R31735, R50548, R50646, R64321, R64322, R75660, R75768, R75866, R76038, R79765, R79766, H22209, H24391, H25902, H27236, H28585, H29860, H29954, H41994, H42226, H42298, H43069, H43893, H43934, R83465, R84983, R94905, R94988, R96360, R96403, R97059, R98674, R98900, R99186, R99187, H50701, H50801, H57754, H62182, H63649, H63650, H64755, H64756, H69075, H70056, H70057, H70855, H70856, H71581, H75758, H75893, H80974, H80975, H83141, H83142, H83271, H85046, H84668, H91780, H92207, H92350, H94891, H94943, H94966, H95486, H99418, N52264, N58261, N74184, N77638, N81021, N92261, N99137, W04350, W07850, W16893, W39467, W45038, W47174, W47433, W52853, W63782, W67635, W67759, W67868, W67881, W93706, W94183, W96351, W96352, N89587, AA012898, AA019884, AA020863, AA025865, AA025866, AA056092, AA057434, AA070445, AA192155, AA192879, AA226741, AA227477
596882	<p>Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1177 of SEQ ID NO:21, b is an integer of 15 to 1191, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:21, and where b is greater than or equal to a + 14.</p>	
616289	<p>Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 839 of SEQ ID NO:22, b is an integer of 15 to 853, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:22, and where b is greater than or equal to a + 14.</p>	
622140	<p>Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide</p>	W39497, W52751, AA099814, AA128882, AA173072, AA226739



	sequence described by the general formula of a-b, where a is any integer between 1 to 460 of SEQ ID NO:23, b is an integer of 15 to 474, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:23, and where b is greater than or equal to a + 14.	
623566	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2266 of SEQ ID NO:24, b is an integer of 15 to 2280, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:24, and where b is greater than or equal to a + 14.	
647714	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1047 of SEQ ID NO:25, b is an integer of 15 to 1061, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:25, and where b is greater than or equal to a + 14.	
647752	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1558 of SEQ ID NO:26, b is an integer of 15 to 1572, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:26, and where b is greater than or equal to a + 14.	
651774	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1991 of SEQ ID NO:27, b is an integer of 15 to 2005, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:27, and where b is greater than or equal to a + 14.	T69901, T69949, T70775, R20554, R33030, R33917, R48406, H58331, H58720, H67041, H68124, H93586, H94430, H94513, H97468, H99219, N23459, N26334, N35428, N49203, N50256, N64246, N93349, W19550, W19996, W25330, W73940, W77984, W93791, W94028, N90424, AA025537, AA025680, AA025371, AA026317, AA026318, AA084549, AA086048, AA086130, AA098995, AA099068, AA115309, AA136486, AA151843, AA149689, AA148825, AA150406, AA150425, AA173377
651995	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1394 of SEQ ID NO:28, b is an integer of 15 to 1408, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:28, and where b is greater than or equal to a + 14.	
652156	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 903 of SEQ ID NO:29, b is an integer of 15 to 917, where both a and	T40364, R22492, R49907, R49908, R62310, R62311, R65652, R67030, R81699, R81700, H18589, H20024, H20099, H20123, H20797, H22404, H22615, H25816, H27051, H42294,

	b correspond to the positions of nucleotide residues shown in SEQ ID NO:29, and where b is greater than or equal to a + 14.	H44827, H49661, H51422, H51465, H56482, H56483, H70295, H86037, H93528, H93860, H96113, H96114, N22715, N31188, N33831, N54495, N70601, N70623, N76607, N78626, W04920, W05505, W07305, W15350, W39442, W60859, W60860, W72726, W76452, AA017463, AA024543, AA024544, AA026421, AA026498, AA027270, AA034429, AA046316, AA046142, AA053920, AA056230, AA063244, AA062885, AA085305, AA128171, AA126216, AA149890, AA150552, AA187825, AA188597, AA417004, AA417190
653010	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 563 of SEQ ID NO:30, b is an integer of 15 to 577, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:30, and where b is greater than or equal to a + 14.	
655904	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2045 of SEQ ID NO:31, b is an integer of 15 to 2059, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:31, and where b is greater than or equal to a + 14.	T61561, T90265, T90707, R09280, R17627, R43348, R54854, R54658, H20872, H27229, H64571, H64673, H64571, N47495, N54722, N75461, W73679, AA010711, AA010712, AA082107, AA130516, AA132052, AA132156, AA147852, AA147908, AA148276, AA148277, AA181933, AA187549, AA187845, AA186675, AA188310, AA193212
657852	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 535 of SEQ ID NO:32, b is an integer of 15 to 549, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:32, and where b is greater than or equal to a + 14.	
666414	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 827 of SEQ ID NO:33, b is an integer of 15 to 841, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:33, and where b is greater than or equal to a + 14.	
667847	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 849 of SEQ ID NO:34, b is an integer of 15 to 863, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:34, and where b is greater than or equal to a + 14.	T47009, T47010, T55133, T55301, T57663, T57702, T59664, T59797, T59800, T49370, T72020, T26631, R22343, R46325, R48879, R50151, R50204, R55208, R71485, R71535, R72144, R72362, R72553, R74062, H13587, H16167, H18121, H20172, H20361, H22514, H40774, H40775,

		H42435, H42865, H43100, H43164, H45140, H45441, H46013, H46083, H46159, R97084, R97131, H56498, H60260, H60567, H67238, H71802, H77325, H77338, H81556, H87775, H87825, H91889, H92057, H93187, H96056, H96420, H81556, H99575, N21484, N23829, N24221, N26831, N27079, N27278, N27582, N30213, N30255, N31642, N31989, N31996, N32655, N32790, N35515, N38983, N39859, N40012, N40488, N41792, N41978, N54988, N57097, N70071, N77176, N78930, N80037, N80573, N81058, N92768, N93810, W07000, W07659, W07868, W44961, W44962, W58175, W58263, W58182, AA001206, AA017579, AA026640, AA026706, AA057605, AA058758, AA082491, AA084088, AA086460, AA100968, AA112029, AA121337, AA121500, AA130704, AA130790, AA152420, AA156094, AA156123, AA181929, AA182575, AA182617, AA186931, AA195982, AA253952, AA283976, AA426098, AA425122, AA428823, AA429359
670188	<p>Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1216 of SEQ ID NO:35, b is an integer of 15 to 1230, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:35, and where b is greater than or equal to a + 14.</p>	
670279	<p>Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 626 of SEQ ID NO:36, b is an integer of 15 to 640, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:36, and where b is greater than or equal to a + 14.</p>	T50781, T51265, T55324, T56327
670729	<p>Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 583 of SEQ ID NO:37, b is an integer of 15 to 597, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:37, and where b is greater than or equal to a + 14.</p>	
674123	<p>Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 610 of SEQ ID NO:38, b is an integer of 15 to 624, where both a and b correspond to the positions of nucleotide residues</p>	

	shown in SEQ ID NO:38. and where b is greater than or equal to a + 14.	
676496	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1015 of SEQ ID NO:39, b is an integer of 15 to 1029, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:39, and where b is greater than or equal to a + 14.	
678162	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1093 of SEQ ID NO:40, b is an integer of 15 to 1107, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:40, and where b is greater than or equal to a + 14.	T40233, T40521, T41098, T47133, T47529, T49156, T49157, T51636, T55352, T55402, T55422, T57649, T59314, T62530, T62806, T62954, T72271, T73592, T89655, T78884, R19194, R89249, R93164, H57861, H93645, N22493, N26661, N32984, N63146, N66448, N67443, N69984, N72141, N77952, N78933, N81091, N95826, W02074, W24850, W24972, W38365, W44897, W57997, W58080, W65414, W65435, W74634, AA007562, AA009767, AA022918, AA022939, AA025169, AA029717, AA029656, AA032096, AA040581, AA046091, AA070493, AA070646, AA070707, AA071405, AA071414, AA074752, AA075706, AA075696, AA079282, AA085620, AA100126, AA126795, AA128838, AA136579, AA143069, AA143200, AA146637, AA147370, AA147705, AA156001, AA157342, AA161090, AA164798, AA179749, AA187235, AA188048, AA187029, AA188384, AA192271, AA196973, AA235468, AA243180, AA459416, AA459642
678248	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1037 of SEQ ID NO:41, b is an integer of 15 to 1051, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:41, and where b is greater than or equal to a + 14.	
683668	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2178 of SEQ ID NO:42, b is an integer of 15 to 2192, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:42, and where b is greater than or equal to a + 14.	T49549, T49550, T49700, T49912, T49937, T50912, T51558, T53285, T53375, T53376, T53721, T54314, T54840, T55217, T56413, T99069, T99669, R01522, R31653, R32820, R32921, R35743, R50997, R64077, R65723, R69349, R71009, R72798, R72824, R76854, R77142, R79240, R79511, R80194, R80295, R81155, H39823, H39824, R84909, R85592, R91193, H50793, H52341, H53594, H53916, H92997, N26572, N32090,

		N32406, N34179, N36271, N45401, N49216, N50267, N67233, N67568, N72254, N75478, N93355, N94504, W00543, W05288, W05816, W23954, W24625, W24650, W25354, W49666, W52302, AA121852, AA121851, AA128593, AA128712, AA136731, AA136688, AA167235, AA167584, AA173693, AA176648, AA176804, AA179999, AA181456, AA181457, AA256158, AA256215, AA256247, AA458729, AA458778, AA464936, AA464937
693172	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 339 of SEQ ID NO:43, b is an integer of 15 to 353, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:43, and where b is greater than or equal to a + 14.	T49005, T50129, T54766, T59468, T71241, T89633, R66699, R67578, H25853, H26090, H41256, H43182, H45273, N58288, N95319, AA054338, AA057604, AA084261
694303	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 3476 of SEQ ID NO:44, b is an integer of 15 to 3490, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:44, and where b is greater than or equal to a + 14.	
695042	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 767 of SEQ ID NO:45, b is an integer of 15 to 781, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:45, and where b is greater than or equal to a + 14.	
699799	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1417 of SEQ ID NO:46, b is an integer of 15 to 1431, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:46, and where b is greater than or equal to a + 14.	T50599, R25615, R31078, R68513, R70896, R75848, R76864, R76865, H01087, H26949, H63077, H75713, H75642, H95014, H98885, N24938, N33815, N47174, N47897, N51152, N53997, N59590, N62387, N63017, N67836, N69948, N78655, N79355, N94343, N98329, W01767, W03440, W15144, W19292, W25534, W37911, W42857, W42912, W48630, W72791, W76438, W81113, W80546, W80525, W80526, W84575, W84645, AA010674, AA011261, AA026981, AA031662, AA039737, AA039810, AA040524, AA040523, AA046308, AA046396, AA099365, AA101915, AA129310, AA129354, AA131951, AA186409
702216	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide	T64167, T64355, T68409, T68475, T73691, T73717, T97735, T97840,

	sequence described by the general formula of a-b, where a is any integer between 1 to 1899 of SEQ ID NO:47, b is an integer of 15 to 1913, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:47, and where b is greater than or equal to a + 14.	T98899, T99491, R00460, R01214, R01326, H45786, R93124, R96609, H61118, H61119, H61454, H62460, H64003, H64052, H91078, H91378, N58480, N64695, N65991, N74260, N78070, N79244, N91708, N95101, W03761, W04301, N90479, AA130077, AA130076, AA152275, AA150441
703015	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1747 of SEQ ID NO:48, b is an integer of 15 to 1761, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:48, and where b is greater than or equal to a + 14.	R72819, R73270, H43839, W47195, W52204, AA242894, AA424584, AA424629
706391	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 942 of SEQ ID NO:49, b is an integer of 15 to 956, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:49, and where b is greater than or equal to a + 14.	T48974, H26922, H30342, H44743, H45233, R88178, H81778, H92363, N29006, N44860, N46515, AA079547, AA158434, AA160590, AA428285
706892	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 549 of SEQ ID NO:50, b is an integer of 15 to 563, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:50, and where b is greater than or equal to a + 14.	
706924	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 3201 of SEQ ID NO:51, b is an integer of 15 to 3215, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:51, and where b is greater than or equal to a + 14.	T68892, T68966, T75421, R15205, R16398, R41650, R42339, R52995, R52996, R41650, H12000, H16753, H16861, H27652, H27653, H27982, H28497, H29323, H29416, H85752, H98511, N22580, N24339, N28586, N42727, N50084, N75803, N78815, W07245, W21306, W23840, W57924, W58128, W72277, W76304, W86460, AA002243, AA002080, AA025565, AA025683, AA026606, AA026718, AA150696, AA150801
707642	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 612 of SEQ ID NO:52, b is an integer of 15 to 626, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:52, and where b is greater than or equal to a + 14.	
710369	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 906 of SEQ ID NO:53, b is an integer of 15 to 920, where both a and	T48815, T60685, T91108, T99835, AA150217, AA157340, AA157240, AA171947

	b correspond to the positions of nucleotide residues shown in SEQ ID NO:53, and where b is greater than or equal to a + 14.	
718826	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1076 of SEQ ID NO:54, b is an integer of 15 to 1090, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:54, and where b is greater than or equal to a + 14.	
719790	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1450 of SEQ ID NO:55, b is an integer of 15 to 1464, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:55, and where b is greater than or equal to a + 14.	T47380, T47538, T47539, T53445, T53446, T54910, T55077, T59959, T60032, T62504, T62649, T63049, T63297, T63382, T65688, T71591, T71742, T93094, T93187, T94131, T94222, T91210, T84959, T99044, T99045, R26119, R26148, R33224, R35866, R36526, R53923, R53924, R69596, R69684, R76209, R76210, R79249, R79521, H03427, H03507, H12529, H13501, H19016, H19310, H21587, H21652, H21653, H30119, H39693, H42698, H46635, R93371, R98210, R99855, H54120, H54786, H54837, H58991, H65355, H65566, H67613, H72632, H74102, H95312, N48235, N58029, N64226, N66907, N70763, N78303, N93848, N94316, N95432, N98433, W01816, W02218, W05772, W21419, W24044, W24297, W30823, W32382, W37228, W37317, W40321, W42528, W46445, W49731, W51944, W53011, W53012, W60051, W60129, W60154, W68332, W68216, W72730, W74593, W92813, W93310, AA010985, AA011307, AA031435, AA035708, AA037040, AA053073, AA053374, AA055567, AA069724, AA069690, AA069682, AA069900, AA069951, AA070693, AA071421, AA074606, AA075555, AA075673, AA075544, AA081017, AA081251, AA081428, AA082119, AA082022, AA082213, AA082241, AA082247, AA082400, AA082365, AA082438, AA082679, AA083225, AA083266, AA083508, AA083411, AA083637, AA084202, AA099623, AA102015, AA099659, AA100102, AA100163, AA100429, AA100430, AA100455, AA100456, AA100711, AA100764, AA100906, AA100919, AA100963, AA101118, AA102494, AA101184, AA112123, AA122359, AA122360, AA126882, AA127103, AA128195, AA128674, AA128686, AA128741.

		AA128747, AA128785, AA133488, AA133489, AA130006, AA130007, AA134211, AA130492, AA130507, AA134345, AA134346, AA134457, AA134458, AA134461, AA134462, AA130907, AA131020, AA131973, AA132141, AA132493, AA132601, AA134904, AA135121, AA135182, AA135348, AA136318, AA143066, AA143256, AA143278, AA143386, AA146650, AA146835, AA146836, AA146860, AA146861, AA146870, AA146871, AA146918, AA147716, AA147707, AA147868, AA148130, AA148090, AA148091, AA152422, AA148435, AA148867, AA148492, AA148702, AA151453, AA151452, AA151828, AA155801, AA155886, AA156025, AA156044, AA156053, AA156155, AA156222, AA157080, AA157168, AA157325, AA157423, AA157434, AA157471, AA157605, AA157631, AA157546, AA157775, AA157826, AA158157, AA158273, AA158888, AA158887, AA159153, AA159250, AA160104, AA159856, AA161278, AA161301, AA160817, AA164741, AA165616, AA165606, AA173037, AA173038, AA176229, AA176317, AA179185, AA179190, AA179200, AA181043, AA181262, AA181342, AA181834, AA181989, AA182794, AA187247, AA187342, AA187379, AA187470, AA187528, AA187740, AA187911, AA188028, AA186378, AA186424, AA186441, AA186442, AA186568, AA186653, AA186661, AA186703, AA186910, AA187081, AA187087, AA187078, AA187135, AA188313, AA188330, AA188342, AA190473, AA193219
720222	<p>Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 971 of SEQ ID NO:56, b is an integer of 15 to 985, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:56, and where b is greater than or equal to a + 14.</p>	AA056718, AA428747
724033	<p>Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1232 of SEQ ID NO:57, b is an integer of 15 to 1246, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:57, and where b is greater than or equal to a + 14.</p>	N50855, AA076233, AA076232



724767	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1952 of SEQ ID NO:58, b is an integer of 15 to 1966, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:58, and where b is greater than or equal to a + 14.	
727065	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1597 of SEQ ID NO:59, b is an integer of 15 to 1611, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:59, and where b is greater than or equal to a + 14.	T26554, R31862, R31869, R67140, R70861, H00137, H23051, H23350, H60670, N28391, N28646, AA081571
727246	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1835 of SEQ ID NO:60, b is an integer of 15 to 1849, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:60, and where b is greater than or equal to a + 14.	
727932	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 219 of SEQ ID NO:61, b is an integer of 15 to 233, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:61, and where b is greater than or equal to a + 14.	
731167	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2319 of SEQ ID NO:62, b is an integer of 15 to 2333, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:62, and where b is greater than or equal to a + 14.	
732514	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1456 of SEQ ID NO:63, b is an integer of 15 to 1470, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:63, and where b is greater than or equal to a + 14.	
734080	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 925 of SEQ ID NO:64, b is an integer of 15 to 939, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:64, and where b is greater than or equal to a + 14.	
734288	Preferably excluded from the present invention are	

	one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2054 of SEQ ID NO:65, b is an integer of 15 to 2068, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:65, and where b is greater than or equal to a + 14.	
739448	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1377 of SEQ ID NO:66, b is an integer of 15 to 1391, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:66, and where b is greater than or equal to a + 14.	T53676, T53677, T54741, T55855, T55906, T56935, T57622, T58975, T58979, T61059, T61143, T90498, T90594, T93775, R07734, R07735, R40067, R75954, R75978, R76790, R76809, R77290, R77315, R77348, R79433, R79434, R97814, H50168, H70091, H77406, H80889, H82088, H82195, N33576, N39028, N48219, N49421, N52598, N66328, N67208, N73788, N78932, N92856, N99411, W07071, W17213, W24422, W25582, W47407, W47574, W49651, W49725, W68140, W68467, AA025829, AA025972, AA074731, AA074835, AA075316, AA081368, AA081369, AA082652, AA082810, AA101054, AA102495, AA115718, AA115719, AA127079, AA127080, AA127200, AA127199, AA128645, AA128813, AA133732, AA130465, AA130466, AA132111, AA143233, AA143289, AA146780, AA147706, AA148134, AA151491, AA157062, AA157046, AA157630, AA165124, AA165123, AA164625, AA165420, AA165583, AA173407, AA173462, AA179910, AA179911, AA180198, AA181087, AA181556, AA182450, AA182951, AA186670, AA188289, AA192925, AA193075, AA464823
739668	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 645 of SEQ ID NO:67, b is an integer of 15 to 659, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:67, and where b is greater than or equal to a + 14.	
740060	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2967 of SEQ ID NO:68, b is an integer of 15 to 2981, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:68, and where b is greater than or equal to a + 14.	
741560	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b,	

	where a is any integer between 1 to 589 of SEQ ID NO:69, b is an integer of 15 to 603, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:69, and where b is greater than or equal to a + 14.	
742543	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1087 of SEQ ID NO:70, b is an integer of 15 to 1101, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:70, and where b is greater than or equal to a + 14.	
742831	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 700 of SEQ ID NO:71, b is an integer of 15 to 714, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:71, and where b is greater than or equal to a + 14.	
745327	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2876 of SEQ ID NO:72, b is an integer of 15 to 2890, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:72, and where b is greater than or equal to a + 14.	
745695	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2474 of SEQ ID NO:73, b is an integer of 15 to 2488, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:73, and where b is greater than or equal to a + 14.	T56303, T58644, T58694, R48815, R48816, R68140, R74376, R78015, R81014, H00852, H01233, H17193, H17969, H25101, H27005, H30607, H41236, H42218, H42290, H42904, H42977, H45271, H45342, R83816, R98855, R98939, H53696, H62059, H82544, H83097, N40713, N92791, W19377, AA025571, AA053695, AA053675, AA069167, AA069166, AA076604, AA076603, AA079426, AA100088, AA099771, AA130265, AA158402, AA179641, AA235643, AA253454, AA250758, AA458951, AA458978, AA459194, AA419280, AA419329, AA425117, AA430664
750316	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 697 of SEQ ID NO:74, b is an integer of 15 to 711, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:74, and where b is greater than or equal to a + 14.	
750522	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 892 of SEQ ID	

	NO:75, b is an integer of 15 to 906, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:75, and where b is greater than or equal to a + 14.	
750583	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 257 of SEQ ID NO:76, b is an integer of 15 to 271, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:76, and where b is greater than or equal to a + 14.	
751020	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 659 of SEQ ID NO:77, b is an integer of 15 to 673, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:77, and where b is greater than or equal to a + 14.	N80268, N95387, W57806, W63590, AA182782, AA187759, AA199806, AA262640, AA262111, AA262106, AA460214
752196	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 353 of SEQ ID NO:78, b is an integer of 15 to 367, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:78, and where b is greater than or equal to a + 14.	R67541
753084	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1330 of SEQ ID NO:79, b is an integer of 15 to 1344, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:79, and where b is greater than or equal to a + 14.	T93791, T93840, R77826, R78199, R99272, H54274, H65600, H67128, H75533, H75532, H81433, N57836, N58786, N72699, N77475, W02480, W78743, W80625, W90276, AA007397, AA127528, AA127529, AA130419, AA147733, AA150095, AA195008, AA195060
754957	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 3734 of SEQ ID NO:80, b is an integer of 15 to 3748, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:80, and where b is greater than or equal to a + 14.	
756557	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1877 of SEQ ID NO:81, b is an integer of 15 to 1891, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:81, and where b is greater than or equal to a + 14.	
756712	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1940 of SEQ ID NO:82, b is an integer of 15 to 1954, where both a	

	and b correspond to the positions of nucleotide residues shown in SEQ ID NO:82, and where b is greater than or equal to a + 14.	
757414	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 922 of SEQ ID NO:83, b is an integer of 15 to 936, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:83, and where b is greater than or equal to a + 14.	T49651, T49652, T92946, T93013, H02307, H02419, N42072, AA169576
757614	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1499 of SEQ ID NO:84, b is an integer of 15 to 1513, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:84, and where b is greater than or equal to a + 14.	T93709, T96172, H00439, H00480, R85176, H51264, H51834, H53645, H57470, H57991, H73334, N33138, N42318, N94987, AA028955, AA081550, AA082013, AA113225, AA113810, AA133619, AA133522, AA132699, AA132810, AA151877, AA149662, AA157324, AA157422, AA159905, AA165014, AA165442, AA165443, AA167837, AA166621, AA166924, AA195339, AA195338, AA252790
757815	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1284 of SEQ ID NO:85, b is an integer of 15 to 1298, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:85, and where b is greater than or equal to a + 14.	
759878	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1995 of SEQ ID NO:86, b is an integer of 15 to 2009, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:86, and where b is greater than or equal to a + 14.	
760227	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 520 of SEQ ID NO:87, b is an integer of 15 to 534, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:87, and where b is greater than or equal to a + 14.	
760312	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 4288 of SEQ ID NO:88, b is an integer of 15 to 4302, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:88, and where b is greater than or equal to a + 14.	
766051	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide	T57753, T60650, R11036, R11084, R00826, R01482, H87221, N25112,

	sequence described by the general formula of a-b, where a is any integer between 1 to 2768 of SEQ ID NO:89, b is an integer of 15 to 2782, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:89, and where b is greater than or equal to a + 14.	N33451, N42424, N47338, N48186, N62628, N68902, N71490, N78399, N99533, W16943, W78948, W85915, W95743, N89568, AA039230, AA039231, AA047564, AA047582, AA047702, AA047752, AA120926, AA126453, AA135549, AA135529, AA429718
767593	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1023 of SEQ ID NO:90, b is an integer of 15 to 1037, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:90, and where b is greater than or equal to a + 14.	T51635, T57709, T61468, T63793, T63818, T92894, T92984, T94396, T75475, T75508, T87575, T79848, T85949, R25644, R27489, R70702, R78772, H44836, H44835, R84349, R86157, R89703, R99494, H48567, H48836, H57859, H83579, H86373, H86690, H88284, H97937, H98241, H99117, H99249, N24363, N24573, N26374, N27129, N31662, N36546, N40064, N45098, N45108, N53503, N59526, N63219, N64179, N64178, N66660, N70536, N72298, N98943, W02894, W19364, W60295, W60386, W72691, W77806, W93582, W93631, W92326, W92382, N90765, AA001997, AA013356, AA017023, AA017221, AA018780, AA026639, AA026705, AA029569, AA029496, AA029736, AA035387, AA035694, AA044958, AA055558, AA063564, AA100726, AA100744, AA134118, AA130301, AA151965, AA233192, AA253060, AA253117
768053	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1038 of SEQ ID NO:91, b is an integer of 15 to 1052, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:91, and where b is greater than or equal to a + 14.	
768055	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1220 of SEQ ID NO:92, b is an integer of 15 to 1234, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:92, and where b is greater than or equal to a + 14.	T68053, R09316, R09788, T84929, R24826, R66259, R68879, R80029, H00967, H89841, H96162, N39802, N44634, N68319, N70487, N71145, N72732, W01594, W52285, W73342, W85800, AA022906, AA022975, AA031962, AA032044, AA032163, AA037604, AA043694, AA043695, AA044134, AA074287, AA081041, AA081042, AA082218, AA082461, AA082475, AA083977, AA100460, AA155926, AA167365, AA171958, AA173534, AA187036, AA224429
769685	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1557 of SEQ ID	

	NO:93, b is an integer of 15 to 1571, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:93, and where b is greater than or equal to $a + 14$ .	
771920	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1858 of SEQ ID NO:94, b is an integer of 15 to 1872, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:94, and where b is greater than or equal to $a + 14$ .	
772790	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1502 of SEQ ID NO:95, b is an integer of 15 to 1516, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:95, and where b is greater than or equal to $a + 14$ .	
772916	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1756 of SEQ ID NO:96, b is an integer of 15 to 1770, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:96, and where b is greater than or equal to $a + 14$ .	
773225	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 924 of SEQ ID NO:97, b is an integer of 15 to 938, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:97, and where b is greater than or equal to $a + 14$ .	
773632	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 297 of SEQ ID NO:98, b is an integer of 15 to 311, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:98, and where b is greater than or equal to $a + 14$ .	
774364	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 606 of SEQ ID NO:99, b is an integer of 15 to 620, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:99, and where b is greater than or equal to $a + 14$ .	W01405, AA172322
775355	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2497 of SEQ ID NO:100, b is an integer of 15 to 2511, where both a	T49285, T61774, T68350, T68396, T94414, T69842, T81078, R01216, R05674, R21522, R21626, R23745, R23797, R24081, R24137, R24753, R32662, R36359, R45484, R45484,

	and b correspond to the positions of nucleotide residues shown in SEQ ID NO:100, and where b is greater than or equal to a + 14.	R63380, R63433, R70942, R70995, R73973, R78964, H08973, H09543, H16712, H16713, H20846, H20896, R99241, H82276, H82382, H84715, H85367, H85516, H89615, H95047, H96450, H97881, N20953, N21537, N22201, N25769, N29477, N30442, N37087, N42334, N42354, N66424, N66864, N67873, N71242, N73740, N94555, N99903, W45394, W46993, W46961, W46960, W46881, W73247, W90778, AA026678, AA026215, AA043908, AA044414, AA042828, AA062957, AA076063, AA121145, AA121476, AA195131, AA234043, AA234044, AA426421
775844	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2967 of SEQ ID NO:101, b is an integer of 15 to 2981, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:101, and where b is greater than or equal to a + 14.	T73286, T66741, T66742, R12147, R15080, R19321, R39271, R42973, R44589, R44589, H06197, H08725, R94752, H71652, H71653, H79764, H79765, H79770, H79762, H79761, H79771, H92246, H96184, N45199, W93244, W93245, W93258, W93257, W94615, W94654, AA001180, AA039582, AA039689, AA082198, AA157370, AA157869, AA253368
777760	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2790 of SEQ ID NO:102, b is an integer of 15 to 2804, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:102, and where b is greater than or equal to a + 14.	
779837	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 708 of SEQ ID NO:103, b is an integer of 15 to 722, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:103, and where b is greater than or equal to a + 14.	T67628, T72838, H59238, H84693, N80048, W07009, W37555, W39191, N90251, AA057629
780769	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1622 of SEQ ID NO:104, b is an integer of 15 to 1636, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:104, and where b is greater than or equal to a + 14.	T66609, T66610, T83560, R15983, R15984, R35702, R49338, R49338, H11613, R94244, H87098, H87745, W60710, W60772, W94034, AA258151, AA258913, AA425943
781445	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1547 of SEQ ID NO:105, b is an integer of 15 to 1561, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:105, and where b is	



	greater than or equal to $a + 14$ .	
781531	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 472 of SEQ ID NO:106, b is an integer of 15 to 486, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:106, and where b is greater than or equal to $a + 14$ .	
783018	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 786 of SEQ ID NO:107, b is an integer of 15 to 800, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:107, and where b is greater than or equal to $a + 14$ .	R18976
783097	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1044 of SEQ ID NO:108, b is an integer of 15 to 1058, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:108, and where b is greater than or equal to $a + 14$ .	
784198	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1062 of SEQ ID NO:109, b is an integer of 15 to 1076, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:109, and where b is greater than or equal to $a + 14$ .	
784868	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1185 of SEQ ID NO:110, b is an integer of 15 to 1199, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:110, and where b is greater than or equal to $a + 14$ .	
785428	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 3616 of SEQ ID NO:111, b is an integer of 15 to 3630, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:111, and where b is greater than or equal to $a + 14$ .	T47751, T39348, T39359, T98137, T79193, T95760, R16653, R16654, R24052, R24245, R33230, R44846, R50794, R50912, R44846, R60930, R61049, R71116, R71620, R77888, R80860, H00109, H04333, H04688, H05041, H09555, H30257, H30320, H47931, R94218, R99062, R99260, H50702, H50803, H52629, H52628, H54000, H67115, H70269, H83460, H83572, H84911, H99358, N21482, N21632, N24626, N33762, N41609, N67949, N69593, N70188, N71452, N71818, N77888, N79031, N99501, W02150, W03072, W05781, W19647, W19972, W20125, W30896, W33043.

		W33197, W35407, W37262, W39072, W47654, W52846, W56143, W60064, W60074, W65501, W67522, W67591, W69745, W69926, W80811, W94093, W94156, N90996, AA039462, AA040857, AA043084, AA043810, AA053423, AA053042, AA064625, AA064709, AA115540, AA115051, AA120833, AA129500, AA129499, AA146736, AA148602, AA152314, AA150343, AA150620, AA150790, AA157282, AA160296, AA173937, AA173969, AA181340, AA188207, AA186354, AA188646, AA190484, AA199676, AA199677, AA243342, AA250981, AA459647, AA459773, AA460227
785845	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1512 of SEQ ID NO:112, b is an integer of 15 to 1526, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:112, and where b is greater than or equal to a + 14.	
785854	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 571 of SEQ ID NO:113, b is an integer of 15 to 585, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:113, and where b is greater than or equal to a + 14.	T85881, W45204
786705	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 487 of SEQ ID NO:114, b is an integer of 15 to 501, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:114, and where b is greater than or equal to a + 14.	R09422
787186	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1951 of SEQ ID NO:115, b is an integer of 15 to 1965, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:115, and where b is greater than or equal to a + 14.	
787279	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1046 of SEQ ID NO:116, b is an integer of 15 to 1060, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:116, and where b is greater than or equal to a + 14.	T62081, T97170, R17585, R42923, R48789, R48896, R54561, R54562, R54721, R54722, R42923, R72984, R73595, H23901, H43508, H46275, H46348, H47255, H47254, R83475, R89352, R91048, R93150, R93669, R94520, R98839, H48417, H48899, H48900, H50560, H54157, H58936,

		H58983, H67630, H69455, H72554, H72955, H89822, N23388, N33070, N35168, N40256, N44641, N52556, N59706, N68387, N80806, N92514, W17007, W19578, W20217, W38835, W49822, W56061, W65416, W65285, N90575, AA002190, AA045344, AA045446, AA052950, AA053432, AA082245, AA083753, AA102071, AA099961, AA101574, AA112070, AA125782, AA125931, AA135139, AA135268, AA146635, AA151603, AA149484, AA149981, AA152120, AA171975, AA172123, AA181805, AA181821, AA188148, AA188225, AA186556, AA186917, AA460297, AA461585
789002	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 695 of SEQ ID NO:117, b is an integer of 15 to 709, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:117, and where b is greater than or equal to a + 14.	
789008	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2039 of SEQ ID NO:118, b is an integer of 15 to 2053, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:118, and where b is greater than or equal to a + 14.	T47492, T47493, T47900, T48303, T48445, T48456, T49007, T49079, T49080, T49218, T49310, T49311, T49913, T49914, T49941, T51256, T51337, T51371, T51423, T51604, T51757, T52271, T52400, T53326, T53327, T54148, T54244, T54295, T54330, T54402, T54407, T55485, T55733, T56237, T56379, T56414, T56565, T39384, T40546, T40551, T40552, T40824, T89603, T79470, T79561, R01378, R12635, R20536, R21209, R21238, R21239, R22062, R22119, R22190, R22241, R22534, R22535, R22823, R23625, R23881, R24090, R25741, R26431, R26587, R28327, R28328, R28330, R31619, R32132, R32349, R33134, R33286, R35454, R36658, R39739, R50498, R50581, R20536, R56656, R65717, R65777, R65870, R67856, R67857, R68076, R69399, R69531, R69752, R69920, R71289, R72350, R74061, R77148, R77149, R80495, R80640, R82550, H00862, H01301, H01472, H01571, H02637, H02893, H03072, H03073, H03443, H03525, H03812, H03836, H23457, H23458, H26513, H26583, H26584, R86226, R86227, R87053, R91130, R91174, R92513, R92642, R93418, R93468, R93700, R94462, R94463, R94793, R95110,

		R96330, R96329, R96675, R96943, R97000, R98195, R99857, H48277, H48366, H48451, H53119, H54247, H54246, H57144, H57217, H58791, H59276, H59324, H59614, H59654, H62873, H62997, H66302, H67109, H67468, H67594, H67634, H67646, H67685, H67891, H67935, H68007, H68476, H72996, H73208, H73882, H74057, H74076, H74196, H75522, H75366, H77704, H77705, H78593, H79262, H79373, H81287, H81343, H82036, H82218, H82313, H87010, H87011, H90552, H90551, H93198, H94403, N28269, N30773, N34862, N38975, N38989, N39317, N43935, N45164, N48122, N48136, N50666, N50756, N52570, N53559, N53589, N55006, N55026, N57654, N58258, N58340, N58627, N58738, N70218, N72552, N72649, N77216, N77511, N77635, N80637, W01074, W58701, W68231, W68232, W68700, W72561, W72580, W72399, W76223, W85725, W92304, W92318, W92144, W92354, AA004478, AA004551, AA009715, AA009825, AA024464, AA024465, AA025660, AA039523, AA039522, AA040081, AA040128, AA040033, AA040827, AA045744, AA053323, AA099152, AA099250
789555	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1810 of SEQ ID NO:119, b is an integer of 15 to 1824, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:119, and where b is greater than or equal to a + 14.	T85669, H62189, H62190, H73963, H73295, N74147, W04314, W23625, W35215, AA040573, AA040671
789631	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 592 of SEQ ID NO:120, b is an integer of 15 to 606, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:120, and where b is greater than or equal to a + 14.	
789779	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 824 of SEQ ID NO:121, b is an integer of 15 to 838, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:121, and where b is greater than or equal to a + 14.	N69694, AA151932
790387	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide	H19654, H87102, H87749, N29354, N34298, N44187, N57052, W69612,

	sequence described by the general formula of a-b, where a is any integer between 1 to 642 of SEQ ID NO:122, b is an integer of 15 to 656, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:122, and where b is greater than or equal to a + 14.	W93844, W93865, AA027893, AA029638, AA058317, AA058495, AA179870, AA232827, AA233881, AA235809
790461	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1372 of SEQ ID NO:123, b is an integer of 15 to 1386, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:123, and where b is greater than or equal to a + 14.	R66275, R76171, R82537, AA054476, AA056199, AA127010, AA143025, AA151006, AA150976
790931	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 831 of SEQ ID NO:124, b is an integer of 15 to 845, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:124, and where b is greater than or equal to a + 14.	T92052, R10686, T84927, R21818, R22331, R22332, R22401, R23139, R23140, R23369, R32153, R32154, R63527, R63575, R68799, R68901, R80768, H12779, H12836, H56522, H56704, H94832, H96055, H96058, H96422, H96418, N26715, N27088, N31910, N32532, N33383, N34596, N42693, N42748, W32121, W37432, W44577, W44627, W51792, W61294, W65390, AA026773, AA026774
791176	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1642 of SEQ ID NO:125, b is an integer of 15 to 1656, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:125, and where b is greater than or equal to a + 14.	T51708, T51919, T69384, R50942, R73632, R73706, H28125, N22822, N78772
791983	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 823 of SEQ ID NO:126, b is an integer of 15 to 837, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:126, and where b is greater than or equal to a + 14.	
792539	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1203 of SEQ ID NO:127, b is an integer of 15 to 1217, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:127, and where b is greater than or equal to a + 14.	H53623, H53662, N23079, N69293, N89689, AA034518, AA035409, AA035410, AA046490, AA046762, AA085037, AA085105, AA134976, AA135078, AA459951, AA460040
792749	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1335 of SEQ ID NO:128, b is an integer of 15 to 1349, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:128, and where b is greater than or equal to a + 14.	R13058, R13951, R40011, R51765, R51766, R40011, R67629, R67630, H01808, H29310, H29403, R99196, H52742, H52788, H61636, H71767, H71768, N20919, N27779, N36030, N41741, N47900, N55480, N76967, W21551, W44410, W44331, W46458, W46528, W46810, W46928, W51766,

		W57869, W58140, W86456, N90422, AA029174, AA029253, AA031374, AA031375, AA062913, AA082549, AA133965, AA167773, AA166872, AA176295, AA176395, AA428235
792961	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2304 of SEQ ID NO:129, b is an integer of 15 to 2318, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:129, and where b is greater than or equal to a + 14.	
793206	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2135 of SEQ ID NO:130, b is an integer of 15 to 2149, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:130, and where b is greater than or equal to a + 14.	
793249	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1006 of SEQ ID NO:131, b is an integer of 15 to 1020, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:131, and where b is greater than or equal to a + 14.	T48358, T48359, T71001, T71063, T72193, T72972, T67531, T69528, T86709, T86804, T89854, T90890, T91159, T85694, T85895, T95466, T95467, R00007, R00008, R12353, R23932, R23933, R37279, R63973, R64080, R73825, R73826, R76905, R77073, R77445, R77538, R79797, R79808, R79894, R79908, H11925, H11926, H15192, H16754, H16862, H19737, H20072, H21725, H22675, H24523, H26125, H26391, H39766, H41271, H41373, H41374, H43544, H43545, H44881, H45180, H45181, R92671, R94833, H57801, H58122, H58123, H62248, H62337, H69587, H69586, H80840, H80930, H85462, H85747, H86829, H86902, H96591, H96708, H97829, H99614, N25266, N26147, N27161, N29792, N33452, N33767, N33906, N36535, N38816, N39177, N40101, N42935, N42425, N44530, N45252, N45445, N57801, N59012, N78685, N79046, N91819, N98480, W02726, W04566, W15191, W15596, W17335, W24253, W25723, W30937, W31253, W31429, W31674, W39685, W44989, W46619, W46654, W57768, W57804, W57841, W57622, W67135, W67136, W73878, W73364, W73441, W77815, W80810, W80903, W92682, W92512, W92513, W96375, W96526, AA001447, AA001482, AA021374, AA021375, AA037268, AA037489, AA037569, AA039708, AA040262, AA040417, AA057011,

		AA074646, AA074679, AA075303, AA088467, AA098947, AA100987, AA126026, AA126122, AA126778, AA128010, AA128034, AA136619, AA136750, AA143234, AA143291, AA143564, AA143565, AA146915, AA151446, AA151447, AA156218, AA157383, AA159151, AA173294, AA179768, AA180442, AA181155, AA181156, AA181722, AA186611, AA188254, AA190686, AA191758, AA191547, AA195441, AA223540, AA223587
793626	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2305 of SEQ ID NO:132, b is an integer of 15 to 2319, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:132, and where b is greater than or equal to a + 14.	
794417	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1359 of SEQ ID NO:133, b is an integer of 15 to 1373, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:133, and where b is greater than or equal to a + 14.	
795197	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1643 of SEQ ID NO:134, b is an integer of 15 to 1657, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:134, and where b is greater than or equal to a + 14.	
795251	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2346 of SEQ ID NO:135, b is an integer of 15 to 2360, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:135, and where b is greater than or equal to a + 14.	T89826, T74514, T89080, R24028, H03686, H97493, N54611, W94797, W94798, AA129537, AA190765, AA191357, AA256363, AA425151, AA429405
795752	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1028 of SEQ ID NO:136, b is an integer of 15 to 1042, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:136, and where b is greater than or equal to a + 14.	
796261	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1023 of SEQ ID	

	NO:137. b is an integer of 15 to 1037, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:137, and where b is greater than or equal to $a + 14$ .	
796933	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1476 of SEQ ID NO:138. b is an integer of 15 to 1490, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:138, and where b is greater than or equal to $a + 14$ .	
799424	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1670 of SEQ ID NO:139. b is an integer of 15 to 1684, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:139, and where b is greater than or equal to $a + 14$ .	
799698	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 413 of SEQ ID NO:140. b is an integer of 15 to 427, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:140, and where b is greater than or equal to $a + 14$ .	
800351	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 875 of SEQ ID NO:141. b is an integer of 15 to 889, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:141, and where b is greater than or equal to $a + 14$ .	
800573	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1491 of SEQ ID NO:142. b is an integer of 15 to 1505, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:142, and where b is greater than or equal to $a + 14$ .	
805815	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1221 of SEQ ID NO:143. b is an integer of 15 to 1235, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:143, and where b is greater than or equal to $a + 14$ .	
806445	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1406 of SEQ ID NO:144. b is an integer of 15 to 1420, where both a	



	and b correspond to the positions of nucleotide residues shown in SEQ ID NO:144, and where b is greater than or equal to a + 14.	
810309	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1905 of SEQ ID NO:145, b is an integer of 15 to 1919, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:145, and where b is greater than or equal to a + 14.	
811022	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1365 of SEQ ID NO:146, b is an integer of 15 to 1379, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:146, and where b is greater than or equal to a + 14.	
811023	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 500 of SEQ ID NO:147, b is an integer of 15 to 514, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:147, and where b is greater than or equal to a + 14.	
811143	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2044 of SEQ ID NO:148, b is an integer of 15 to 2058, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:148, and where b is greater than or equal to a + 14.	
811381	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1767 of SEQ ID NO:149, b is an integer of 15 to 1781, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:149, and where b is greater than or equal to a + 14.	
811595	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1695 of SEQ ID NO:150, b is an integer of 15 to 1709, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:150, and where b is greater than or equal to a + 14.	T51013, T51104, T54094, T54185, T68577, T68655, T90261, T90702, T92691, R34639, R49168, R51392, R49168, R84952, R84994, H84723, H84890, N29820, N42512, N64677, N67206, N73458, N80110, N92710, W02861, W20327, W23680, W76675, AA031294, AA062736, AA062781, AA070243, AA070244, AA084464, AA100714, AA100767, AA136726, AA136684, AA191613, AA223541, AA223589, AA252636
813000	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide	

	sequence described by the general formula of a-b, where a is any integer between 1 to 908 of SEQ ID NO:151, b is an integer of 15 to 922, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:151, and where b is greater than or equal to a + 14.	
813288	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 621 of SEQ ID NO:152, b is an integer of 15 to 635, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:152, and where b is greater than or equal to a + 14.	
813431	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2314 of SEQ ID NO:153, b is an integer of 15 to 2328, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:153, and where b is greater than or equal to a + 14.	T94237, T89464, T89552, R09285, T78198, R14453, R15241, R15311, R21130, R33140, R33292, R40972, R46726, R42211, R40972, R46726, R66207, R67085, R73679, R73770, H12485, H19135, H22930, H24111, H26774, H26884, R89854, R89894, R92012, R92057, H53798, H61991, H61992, H64854, H65452, H73213, H74063, H79753, H79754, H80620, H80654, H81209, H81210, H84019, H84020, N35581, N68664, N73792, N91681, N92730, N99417, W20349, W46901, W52684, W60422, W61136, W61108, W61174, W68119, W73989, W79021, W79231, W80414, W80777, W80930, AA040315, AA045023, AA045024, AA045188, AA045352, AA181735, AA181799, AA223229, AA223428, AA464186, AA464780, AA428152, AA430305
813450	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1254 of SEQ ID NO:154, b is an integer of 15 to 1268, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:154, and where b is greater than or equal to a + 14.	T90954, T84401, T85262, R22109, R48652, R72000, R73453, H14261, H27403, H42017, H42018, H38149, H38150, H69302, H69397, N98775, AA148803, AA150212
813478	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 4285 of SEQ ID NO:155, b is an integer of 15 to 4299, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:155, and where b is greater than or equal to a + 14.	
813505	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 992 of SEQ ID NO:156, b is an integer of 15 to 1006, where both a and b correspond to the positions of nucleotide	

	residues shown in SEQ ID NO:156, and where b is greater than or equal to a + 14.	
815552	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1672 of SEQ ID NO:157, b is an integer of 15 to 1686, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:157, and where b is greater than or equal to a + 14.	
815606	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 4133 of SEQ ID NO:158, b is an integer of 15 to 4147, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:158, and where b is greater than or equal to a + 14.	T69152, T69213, T80080, T80327, R19043, R27520, R38534, R38898, R44031, R44031, R67769, H11493, H11852, H13644, H22161, H28042, H39529, H42500, H43488, N32678, N50022, N51861, N54126, N54677, W16972, W32896, W35293, W38598, N89624, N90277, AA027830, AA027892, AA035739, AA055806, AA069223, AA078890, AA078891, AA099437, AA099478, AA101431, AA112543, AA121794, AA129629, AA136251, AA143110, AA150576, AA157125, AA158242, AA158709, AA159976, AA160357, AA159491, AA160534, AA160629, AA165150, AA165151, AA164643, AA166799, AA169647, AA169822, AA173082, AA187009, AA224150, AA224303, AA224514, AA224513, AA224488, AA226779, AA227396, AA227518, AA232104, AA232580, AA256938, AA255494, AA429442
816048	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1228 of SEQ ID NO:159, b is an integer of 15 to 1242, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:159, and where b is greater than or equal to a + 14.	T54940, T59322, R35627, R46514, R48419, R48536, R48537, R48569, R48582, R48668, R48683, R49781, R49827, R53111, R53210, R66870, R67958, R69435, R69517, R70414, R71907, R71948, R72113, R72818, R73269, R75924, R75959, R79565, R79566, R80393, H25645, H26211, H29817, H29904, H39626, H39738, H39881, H40715, H42210, H42281, H42354, H42710, H43124, R83615, R86066, R92103, R92104, R96726, R96727, H54075, H54232, H54233, H62253, H62342, H80441, H80442, H91114, H97541, H99927, N27357, N27665, N93636, W19226, W19703, W25418, W25514, W44404, W63554, W78078, N89960, AA027093, AA027132, AA045021, AA045022, AA045721, AA045720, AA046247, AA046280, AA058624, AA074786, AA074787, AA082394, AA085101, AA085282, AA100996, AA127562, AA127729, AA127784, AA128372,

		AA134954, AA143611, AA148145, AA150570, AA161257, AA182028, AA188387, AA232423, AA464270, AA464381, AA421219, AA425804, AA428372
822978	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2215 of SEQ ID NO:160, b is an integer of 15 to 2229, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:160, and where b is greater than or equal to a + 14.	R28400, R82355, R82411, H01338, H01388, N24952, N33829, AA043471, AA043472, AA125807, AA128280, AA129405, AA133871, AA129367, AA133179, AA133312, AA131385, AA428408
823616	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1906 of SEQ ID NO:161, b is an integer of 15 to 1920, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:161, and where b is greater than or equal to a + 14.	
823981	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2605 of SEQ ID NO:162, b is an integer of 15 to 2619, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:162, and where b is greater than or equal to a + 14.	
824364	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1405 of SEQ ID NO:163, b is an integer of 15 to 1419, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:163, and where b is greater than or equal to a + 14.	R21933, H39733, N69879, AA027031, AA100964, AA157234, AA173338
824423	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 3796 of SEQ ID NO:164, b is an integer of 15 to 3810, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:164, and where b is greater than or equal to a + 14.	
825279	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 803 of SEQ ID NO:165, b is an integer of 15 to 817, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:165, and where b is greater than or equal to a + 14.	R06729, R61520, R86829, H51131, N57993, W93696, AA423827
825442	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1564 of SEQ ID	

	NO:166, b is an integer of 15 to 1578, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:166, and where b is greater than or equal to a + 14.	
825548	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1680 of SEQ ID NO:167, b is an integer of 15 to 1694, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:167, and where b is greater than or equal to a + 14.	
825725	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1622 of SEQ ID NO:168, b is an integer of 15 to 1636, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:168, and where b is greater than or equal to a + 14.	
826639	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 653 of SEQ ID NO:169, b is an integer of 15 to 667, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:169, and where b is greater than or equal to a + 14.	
827079	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 3584 of SEQ ID NO:170, b is an integer of 15 to 3598, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:170, and where b is greater than or equal to a + 14.	
827153	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 926 of SEQ ID NO:171, b is an integer of 15 to 940, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:171, and where b is greater than or equal to a + 14.	
827351	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1444 of SEQ ID NO:172, b is an integer of 15 to 1458, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:172, and where b is greater than or equal to a + 14.	R14710, H92769, H92882, AA195498, AA242878, AA242884, AA252152, AA251967, AA465181, AA465542, AA481105, AA481210, AA492206, AA732326
827503	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2695 of SEQ ID NO:173, b is an integer of 15 to 2709, where both a	

	and b correspond to the positions of nucleotide residues shown in SEQ ID NO:173, and where b is greater than or equal to $a + 14$ .	
827563	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 999 of SEQ ID NO:174, b is an integer of 15 to 1013, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:174, and where b is greater than or equal to $a + 14$ .	
827565	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1683 of SEQ ID NO:175, b is an integer of 15 to 1697, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:175, and where b is greater than or equal to $a + 14$ .	
827893	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1395 of SEQ ID NO:176, b is an integer of 15 to 1409, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:176, and where b is greater than or equal to $a + 14$ .	
828072	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1489 of SEQ ID NO:177, b is an integer of 15 to 1503, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:177, and where b is greater than or equal to $a + 14$ .	R20502, R45322, R45322, H29062, H29165, N36388, N39601, AA043930, AA044003, AA115568, AA115087, AA232982, AA234020, AA251431, AA251432, AA459761, AA768137, AA830696, AA918618, AA977409
828228	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1364 of SEQ ID NO:178, b is an integer of 15 to 1378, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:178, and where b is greater than or equal to $a + 14$ .	T76992, T83862, R37649, R68086, R68125, H05325, H05379, H11520, H60866, N27826, N59149, N71661, AA004459, AA004512, AA026983, AA031653, AA045803, AA045870, AA127220, AA126199, AA129772, AA133788, AA131742, AA166788, AA216416, AA229513, AA469120, AA469189, AA503687, AA516488, AA522741, AA542827, AA614664, AA847108, AA876618, AA886579, AA887825, AA888263, AA888262, AA934459, N31217, D79619, N55800, AA026982, AA031743
828241	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2237 of SEQ ID NO:179, b is an integer of 15 to 2251, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:179, and where b is greater than or equal to $a + 14$ .	R09047, H71262, N28995, W07805, W89157, AA007537, AA203119

828287	<p>Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 986 of SEQ ID NO:180, b is an integer of 15 to 1000, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:180, and where b is greater than or equal to a + 14.</p>	R00158, R34699, R34806, R55812, R55897, H02931, H04234, H38596, H38841, H38877, R84345, R84762, R85507, H51401, N22910, N31298, N36027, N64463, N70710, N80820, N94519, N99846, W15234, W15579, W15620, W23968, W24669, W30920, W31655, W37399, W37400, W39182, W45512, W44342, W45653, W44569, W44608, W47630, W47631, W52183, W52421, W57603, W58189, W58466, W60614, W73715, W78044, W90451, W90258, W92042, W91902, AA012954, AA013060, AA013459, AA013460, AA018132, AA018050, AA021226, AA021359, AA021556, AA021640, AA033802, AA040580, AA040552, AA047883, AA054092, AA055181, AA055893, AA082252, AA082502, AA099128, AA099165, AA100988, AA131285, AA136296, AA136178, AA151469, AA151470, AA156144, AA158033, AA158325, AA164422, AA164402, AA167105, AA182609, AA182541, AA187289, AA187406, AA523678, AA582094, AA570257, AA573999, AA574305, AA579097, AA661683, AA662869, AA664665, AA736798, AA770689, AA865267, AA902336, AA923648, AA933570, AA939196, AA988468, A1000226, A1089764, D79059, N84733, W73650, N86290, N88454, C04677, C06015, AA033803, R29541, AA089664, AA089996, C17096, C17255, C19033, AA093458
828364	<p>Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1415 of SEQ ID NO:181, b is an integer of 15 to 1429, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:181, and where b is greater than or equal to a + 14.</p>	R55711, R55921, R68105, R68149, R72479, R72941, N70480, W72759
828371	<p>Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2711 of SEQ ID NO:182, b is an integer of 15 to 2725, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:182, and where b is greater than or equal to a + 14.</p>	T62048, T62112, T91683, T92364, T92416, T93284, N49690, N49793, N64329, N80813, W15549, W15404, W31643, W53039, W92220, W92342, AA055521, AA055520, AA149883, AA150063, AA148836, AA150436
828403	<p>Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1737 of SEQ ID NO:183, b is an integer of 15 to 1751, where both a</p>	AA485171, AA515218, AA603721, AA612760, AA838541, AA970526, C18512

	and b correspond to the positions of nucleotide residues shown in SEQ ID NO:183, and where b is greater than or equal to a + 14.	
828501	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2186 of SEQ ID NO:184, b is an integer of 15 to 2200, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:184, and where b is greater than or equal to a + 14.	H19145, N75547, AA044653, AA128979, AA159576, AA423963, AA523306, H62675, H97872, AA610503, AA010941, AA011327, AA043344
828520	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1973 of SEQ ID NO:185, b is an integer of 15 to 1987, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:185, and where b is greater than or equal to a + 14.	H70392, N30525, N30537, AA010769, AA463668, AA927343, AA091744
828527	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1723 of SEQ ID NO:186, b is an integer of 15 to 1737, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:186, and where b is greater than or equal to a + 14.	T39306, T40514, R08857, R08964, R00734, R00735, R13824, R20172, R37684, R44959, R44959, H05503, H17017, H17018, H54295, H54372, H54503, H67654, H67974, H87993, N33311, N37017, N44843, N55182, N75469, N75534, N77241, N93004, W05278, W05327, W45465, W88760, W88865, AA010623, AA010624, AA234956, AA235130, AA424457, AA282705, AA283023, AA283109, AA481529, AA481595, AA490727, AA491218, AA554176, AA614573, AA665370, AA687964, AA736921, AA765107, AA767430, AA809487, AA865595, N88052
828538	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1118 of SEQ ID NO:187, b is an integer of 15 to 1132, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:187, and where b is greater than or equal to a + 14.	
828541	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1253 of SEQ ID NO:188, b is an integer of 15 to 1267, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:188, and where b is greater than or equal to a + 14.	
828549	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 3773 of SEQ ID NO:189, b is an integer of 15 to 3787, where both a and b correspond to the positions of nucleotide	



	residues shown in SEQ ID NO:189, and where b is greater than or equal to $a + 14$ .	
828562	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 540 of SEQ ID NO:190, b is an integer of 15 to 554, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:190, and where b is greater than or equal to $a + 14$ .	
828576	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 860 of SEQ ID NO:191, b is an integer of 15 to 874, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:191, and where b is greater than or equal to $a + 14$ .	
828602	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2089 of SEQ ID NO:192, b is an integer of 15 to 2103, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:192, and where b is greater than or equal to $a + 14$ .	
828628	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1303 of SEQ ID NO:193, b is an integer of 15 to 1317, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:193, and where b is greater than or equal to $a + 14$ .	
828667	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1238 of SEQ ID NO:194, b is an integer of 15 to 1252, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:194, and where b is greater than or equal to $a + 14$ .	
828684	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1674 of SEQ ID NO:195, b is an integer of 15 to 1688, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:195, and where b is greater than or equal to $a + 14$ .	R11676, R12284, N68621, N71575, N99448, W02008, W58632, W74361, W76341, W78934, W85701, AA070898, AA070787, AA102636, AA102661, AA102678, AA190864, AA190957, AA197279, AA251577, AA464994, AA421724, AA470741, AA505341, AA506137, AA583780, AA579967, AA714136, AA743352, AA747903, AA814422, AA826755, AA836633, AA837944, AA936844, A1004160, C00265, AA641021
828727	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b,	R35925, R35954, R49443, R49468, R49443, R49468, N74960, AA083678, AA086366, AA100585, AA111863,

	where a is any integer between 1 to 742 of SEQ ID NO:196, b is an integer of 15 to 756, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:196, and where b is greater than or equal to a + 14.	AA156573, AA159175, AA192611, AA195925, AA195976, AA418567, AA418582
828734	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1457 of SEQ ID NO:197, b is an integer of 15 to 1471, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:197, and where b is greater than or equal to a + 14.	
828750	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 678 of SEQ ID NO:198, b is an integer of 15 to 692, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:198, and where b is greater than or equal to a + 14.	
828842	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1559 of SEQ ID NO:199, b is an integer of 15 to 1573, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:199, and where b is greater than or equal to a + 14.	R31695, R31737, R86919, R86763, H66952, N30849, N41376, N95538, W03782, W24227, N90171, AA020001, AA046039, AA046149, AA099753, AA489705, AA552582, AA580818, AA584291, AA730113, AA910268
828843	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2728 of SEQ ID NO:200, b is an integer of 15 to 2742, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:200, and where b is greater than or equal to a + 14.	T57326, T57387, T94838, T94837, T94879, T94925, T74456, R11995, R15234, R19543, R21728, R36670, R39752, R39834, R40808, R40808, R43895, R70936, R70988, R74057, R74152, R79967, R80062, H02983, H04277, H08966, H09537, H25298, H25343, H25449, H25495, H29439, H29438, H29887, H29987, R86318, H65676, H87966, H88350, H97859, N20316, N26629, N27590, N39724, N52972, W39188, W45099, W45149, N90248, AA004834, AA033776, AA039900, AA039901, AA041524, AA044928, AA082729, AA085742, AA112974, AA128343, AA133157, AA171997, AA418609, AA418664, AA421626, AA430065, AA230107, AA230108, AA513630, AA521134, AA622056, AA635868, AA639882, AA714929, AA715480, AA715556, AA729814, AA731061, AA811597, AA830222, AA873240, AA886078, AA886270, AA907208, AA932201, AA977447, AA989000, D81476, N56281, C21262, AA089709
828851	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide	

	sequence described by the general formula of a-b, where a is any integer between 1 to 1403 of SEQ ID NO:201, b is an integer of 15 to 1417, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:201, and where b is greater than or equal to a + 14.	
828856	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1498 of SEQ ID NO:202, b is an integer of 15 to 1512, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:202, and where b is greater than or equal to a + 14.	
828862	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 405 of SEQ ID NO:203, b is an integer of 15 to 419, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:203, and where b is greater than or equal to a + 14.	AA021223
828870	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2819 of SEQ ID NO:204, b is an integer of 15 to 2833, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:204, and where b is greater than or equal to a + 14.	
828873	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 5816 of SEQ ID NO:205, b is an integer of 15 to 5830, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:205, and where b is greater than or equal to a + 14.	
828892	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 741 of SEQ ID NO:206, b is an integer of 15 to 755, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:206, and where b is greater than or equal to a + 14.	R54649, W46198
828893	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1982 of SEQ ID NO:207, b is an integer of 15 to 1996, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:207, and where b is greater than or equal to a + 14.	
828897	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b,	

	where a is any integer between 1 to 1654 of SEQ ID NO:208, b is an integer of 15 to 1668, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:208, and where b is greater than or equal to a + 14.	
828910	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2236 of SEQ ID NO:209, b is an integer of 15 to 2250, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:209, and where b is greater than or equal to a + 14.	T91595, T65436, T65518, T70584, T70847, T75377, R09159, R09261, R09950, T96365, T96446, R12590, R13068, R18120, R21193, R22430, R22480, R22810, R25025, R26742, R26976, R32026, R32079, R33017, R33904, R36588, R39200, R40499, R45972, R40499, R45972, R56330, R64494, R65591, R67446, R70974, R74477, R74579, R77932, R78301, R78497, R78547, R80142, R80143, H00643, H00729, H03024, H04306, H06614, H07124, H09643, H09677, H28706, H28835, H42802, H47310, R92010, H65658, H65657, H67068, H68151, H71685, H72248, H72786, H72785, H73342, H75583, H75514, H77433, H98557, N20087, N22979, N23822, N28617, N29593, N32509, N33262, N40705, N42724, N44752, N45195, N57760, N58105, N59101, N59726, N64423, N66868, N71993, N73995, N99375, W01801, W02025, W19280, W19667, W19930, W25451, W25645, W31475, W31938, W32153, W32005, W37711, W37710, W46758, W46905, W49818, W56089, W57771, W57844, W61375, W61376, W60415, W60416, W61142, W61190, W67942, W67941, W74649, W84332, W84393, W86146, W94323, AA016041, AA015933, AA022593, AA022594, AA030003, AA043309, AA069392, AA069393, AA069775, AA069812, AA102392, AA112674, AA112673, AA135337, AA135336, AA143448, AA152405, AA152459, AA149804, AA149829, AA149849, AA149856, AA156559, AA157731, AA159045, AA160734, AA173662, AA173661, AA235812, AA242974, AA243081, AA242998, AA252146, AA460003, AA460542, AA428205, AA429142, AA285041, AA283758, AA283993, AA480305, AA506566, AA524852, AA631324, AA575859, AA658502, AA766717, AA808234, AA837876, AA866075, AA877425, AA879058, AA886608, AA902179, AA904000, AA928667, AA937136, AA962263, AA995987, AI024986, W25995, W26229, W27231, W26246, W28106,

		W28807, W48809, C01974, AA640952, C14885, C15137
828927	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 824 of SEQ ID NO:210, b is an integer of 15 to 838, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:210, and where b is greater than or equal to a + 14.	
828932	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1199 of SEQ ID NO:211, b is an integer of 15 to 1213, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:211, and where b is greater than or equal to a + 14.	T50679, T51209, T78077, R42605, R48768, R42605, R91277, H61157, W38635, W44738, W46899, W80700, AA017684, AA017707, AA018069, AA019662, AA040254, AA053989, AA054041, AA070137, AA070138, AA074661, AA086354, AA158859, AA223111, AA224210, AA224315, AA232155, AA471047, AA588037, AA720832, AA872503
828933	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 955 of SEQ ID NO:212, b is an integer of 15 to 969, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:212, and where b is greater than or equal to a + 14.	
828941	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1680 of SEQ ID NO:213, b is an integer of 15 to 1694, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:213, and where b is greater than or equal to a + 14.	
828957	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1196 of SEQ ID NO:214, b is an integer of 15 to 1210, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:214, and where b is greater than or equal to a + 14.	R09987, R16645, R16734, R81727, H58067, H58066, H59815, H59816, H64860, H65458, N70923, W81647, W81187, AA052891, AA053046, AA251319, AA251723, AA262259, AA262870, AA463359, AA463865, AA417918, AA418169, AA480203, AA521273, AA836429, AA858135, AA888105, AA917914, AA937591, AA947712, AA961752, AA973797, A1085881
828963	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1762 of SEQ ID NO:215, b is an integer of 15 to 1776, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:215, and where b is greater than or equal to a + 14.	
828964	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide	

	sequence described by the general formula of a-b, where a is any integer between 1 to 1404 of SEQ ID NO:216, b is an integer of 15 to 1418, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:216, and where b is greater than or equal to a + 14.	
828966	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2186 of SEQ ID NO:217, b is an integer of 15 to 2200, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:217, and where b is greater than or equal to a + 14.	T57322, T57383, R07432, R07433, R24183, R37889, R64196, R64212, H10798, H16281, H96182, N24864, N31801, N31897, N51466, N53607, N71323, N71374, N71696, N78973, N91801, N99595, N99806, W17338, W38617, W44695, W52815, W93325, W95029, AA027074, AA031625, AA031706, AA034522, AA101476, AA101477, AA156927, AA157179, AA173234, AA196758, AA506558, AA541561, AA552220, AA573198, AA687807, AA732065, AA769029, AA804914, AA858375, AA931935, AA995830, A1075078, A1075079, AA641307
828967	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1839 of SEQ ID NO:218, b is an integer of 15 to 1853, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:218, and where b is greater than or equal to a + 14.	T86194, T99270, R00981, R21065, R28076, R28291, R46245, R46245, R61751, R61752, H20415, H41325, H46347, H46354, W01107, W96450, W96548, AA082920, AA192528, AA494252, AA507548, AA604189, AA604361, AA614008, AA622126, AA573865, AA578191, AA568157, AA780392, AA812241, AA830010, AA836096, AA876742, C21216
828977	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1079 of SEQ ID NO:219, b is an integer of 15 to 1093, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:219, and where b is greater than or equal to a + 14.	T54853, T55018, T61617, T61701, T71718, T71787, R43855, R43855, H79047, W23509, W78022, AA028959, AA028960, AA035641, AA035749, AA040562, AA042827, AA044641, AA150059, AA459301, AA459532, AA419054, AA532924, AA603462, AA573839, AA863332, AA877269, A1016670, A1083871, A1085531
828978	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2141 of SEQ ID NO:220, b is an integer of 15 to 2155, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:220, and where b is greater than or equal to a + 14.	
828979	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1250 of SEQ ID NO:221, b is an integer of 15 to 1264, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:221, and where b is greater than or equal to a + 14.	

829001	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2071 of SEQ ID NO:222, b is an integer of 15 to 2085, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:222, and where b is greater than or equal to a + 14.	
829003	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2907 of SEQ ID NO:223, b is an integer of 15 to 2921, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:223, and where b is greater than or equal to a + 14.	T56900, T56901, T57894, T57976, T58709, T83854, T83994, T83995, T85283, T85493, T85938, T98545, T98546, R23866, R51491, R51492, R70815, H06524, H06579, H21400, H22212, H26306, H26465, H40800, H42803, H44004, H45104, H45577, R84544, R85933, R95902, R98186, R98187, R99129, H51499, H62734, H62818, H67266, H67280, H67971, H72027, H72028, H86532, H86617, H97834, N22060, N22322, N22927, N23444, N23843, N27358, N27627, N31797, N53099, N55505, N55527, N62760, N76278, N76994, N81072, N99969, W07363, W15385, W30908, W32209, W32266, W37612, W39341, W45721, W44369, W60688, W60728, W74331, W79764, W79508, AA010902, AA011007, AA013382, AA013383, AA017180, AA018376, AA021435, AA128552, AA128295, AA161229, AA160487, AA236095, AA259037, AA458538, AA428449, AA491943, AA492101, AA501898, AA505736, AA551906, AA552335, AA554636, AA564579, AA588897, AA593936, AA595710, AA610733, AA612690, AA569349, AA570259, AA570263, AA573856, AA579746, AA658849, AA721609, AA743280, AA743326, AA808972, AA831035, AA836900, AA887420, AA887859, AA970292, AA994943, AA994947, AI014465, F19724, N36447, D78889, N75198, W37467, W79607, C03008, C04753
829016	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 4381 of SEQ ID NO:224, b is an integer of 15 to 4395, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:224, and where b is greater than or equal to a + 14.	
829027	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 3021 of SEQ ID	

	NO:225, b is an integer of 15 to 3035, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:225, and where b is greater than or equal to a + 14.	
829028	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1497 of SEQ ID NO:226, b is an integer of 15 to 1511, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:226, and where b is greater than or equal to a + 14.	
829031	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2225 of SEQ ID NO:227, b is an integer of 15 to 2239, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:227, and where b is greater than or equal to a + 14.	T52373, T52446, T65540, T91789, R10959, T84998, R06717, R28502, R48288, R48390, R48442, R54616, R54879, R55311, R55316, R55413, R55418, R72602, R72669, R72946, H15595, H27333, H41543, H37781, R84976, R85050, R88513, R88514, H49052, H49116, H96219, H96754, H97979, N23664, N25056, N26150, N32997, N51857, N54122, W65281, W65277, W72409, W76488, W92510, N91031, AA045475, AA056943, AA057662, AA057806, AA126670, AA127032, AA136891, AA137001, AA158595, AA158989, AA279342, AA604130, AA604929, AA631863, C01812
829034	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2332 of SEQ ID NO:228, b is an integer of 15 to 2346, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:228, and where b is greater than or equal to a + 14.	
829036	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2232 of SEQ ID NO:229, b is an integer of 15 to 2246, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:229, and where b is greater than or equal to a + 14.	W19899, W56172, N91246, AA053015, AA258943, AA508101, AA557537, AA744258, C06034, AA053503
829049	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1988 of SEQ ID NO:230, b is an integer of 15 to 2002, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:230, and where b is greater than or equal to a + 14.	
829073	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 980 of SEQ ID	N71827, W07562, W79070, W94296, AA026190, AA215725, AA279902, AA832099



	NO:231, b is an integer of 15 to 994, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:231, and where b is greater than or equal to a + 14.	
829075	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 472 of SEQ ID NO:232, b is an integer of 15 to 486, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:232, and where b is greater than or equal to a + 14.	
829076	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2067 of SEQ ID NO:233, b is an integer of 15 to 2081, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:233, and where b is greater than or equal to a + 14.	
829080	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 502 of SEQ ID NO:234, b is an integer of 15 to 516, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:234, and where b is greater than or equal to a + 14.	
829087	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1115 of SEQ ID NO:235, b is an integer of 15 to 1129, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:235, and where b is greater than or equal to a + 14.	
829092	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1031 of SEQ ID NO:236, b is an integer of 15 to 1045, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:236, and where b is greater than or equal to a + 14.	
829095	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 676 of SEQ ID NO:237, b is an integer of 15 to 690, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:237, and where b is greater than or equal to a + 14.	T98739, T98740, R53404, R72484, H09731, H16600, H21795, H25680, N79773, N93472, AA812105, AA826523, AA954170, A1084914
829096	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1859 of SEQ ID NO:238, b is an integer of 15 to 1873, where both a	T40001, T40939, R53257, R62981, R62980, R63036, H15127, H15187, H24078, H24188, H81472, H88927, H88927, H99390, N32032, N47835, N66666, N98950, AA022842,

	and b correspond to the positions of nucleotide residues shown in SEQ ID NO:238, and where b is greater than or equal to $a + 14$ .	AA022965, AA024917, AA024918, AA035721, AA062907, AA102646, AA101299, AA223395, AA419511, AA421963, AA421964, AA524699, AA532380, AA614315, AA570194, AA742712, AA865440, AA887301, AA987486, AA988144, AA091175
829118	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 891 of SEQ ID NO:239, b is an integer of 15 to 905, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:239, and where b is greater than or equal to $a + 14$ .	
829152	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1470 of SEQ ID NO:240, b is an integer of 15 to 1484, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:240, and where b is greater than or equal to $a + 14$ .	T72498, T73568, T74363, T86984, R10378, R10477, T85969, R05924, R06022, H58205, H65999, H66000, N68870, N92084, N92944, AA188651, AA188754, N72345
829160	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1507 of SEQ ID NO:241, b is an integer of 15 to 1521, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:241, and where b is greater than or equal to $a + 14$ .	R19077, R24890, R70937, R70989, R75822, R75823, H13581, R88030, H97197, H97205, H97610, H97622, H97640, H99011, N22163, N22211, N25706, N31618, N31627, N34096, N35586, N57066, N57078, N57083, N63961, N71248, N71530, N79638, W23686, W25345, W80523, W80524, AA027117, AA044025, AA044347, AA056543, AA056646, AA082122, AA120870, AA120871, AA129173, AA129197, AA173547, AA173713, AA190689, AA252595, AA258865, AA259007, AA576323, AA768606, N55993, N84224
829163	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1130 of SEQ ID NO:242, b is an integer of 15 to 1144, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:242, and where b is greater than or equal to $a + 14$ .	R27150, H50951, N39917, N41848, N41877
829176	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 920 of SEQ ID NO:243, b is an integer of 15 to 934, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:243, and where b is greater than or equal to $a + 14$ .	T46875, T53785, T62036, T73807, R11065, R11122, T84299, T85183, R01714, R02656, R02737, R02738, H41134, H64904, H79712, H79713, N68598, N71315, N71366, N99798, W01984
829204	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b.	R50489, R50573, R74498, R74499, AA234014, AA535362, AA554207, AA847239

	where a is any integer between 1 to 901 of SEQ ID NO:244, b is an integer of 15 to 915, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:244, and where b is greater than or equal to a + 14.	
829207	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1262 of SEQ ID NO:245, b is an integer of 15 to 1276, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:245, and where b is greater than or equal to a + 14.	
829228	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 3352 of SEQ ID NO:246, b is an integer of 15 to 3366, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:246, and where b is greater than or equal to a + 14.	T40764, T49773, T49774, H05098, H49148, H51985, H52105, N36154, N51490, N52526, N53635, AA054314, AA074167, AA152473, AA152472, AA188950, AA278366, AA281330, AA468930, AA469004, AA482010, AA542938, AA554491, AA565215, AA579406, AA741363, AA807139, AA832066, AA836995, AA876036, AA995854
829252	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2134 of SEQ ID NO:247, b is an integer of 15 to 2148, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:247, and where b is greater than or equal to a + 14.	
829254	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2211 of SEQ ID NO:248, b is an integer of 15 to 2225, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:248, and where b is greater than or equal to a + 14.	
829269	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1190 of SEQ ID NO:249, b is an integer of 15 to 1204, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:249, and where b is greater than or equal to a + 14.	
829277	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1300 of SEQ ID NO:250, b is an integer of 15 to 1314, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:250, and where b is greater than or equal to a + 14.	
829290	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide	

	sequence described by the general formula of a-b, where a is any integer between 1 to 1145 of SEQ ID NO:251, b is an integer of 15 to 1159, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:251, and where b is greater than or equal to a + 14.	
829294	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2474 of SEQ ID NO:252, b is an integer of 15 to 2488, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:252, and where b is greater than or equal to a + 14.	
829299	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1540 of SEQ ID NO:253, b is an integer of 15 to 1554, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:253, and where b is greater than or equal to a + 14.	T82894, H25618, N48726, W52191, AA037331, AA223798, AA224330, AA635842, AA748884, AA826495, AA864458, AA903250, AA908466, AA931986, D81481, N56293, C02225
829308	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1492 of SEQ ID NO:254, b is an integer of 15 to 1506, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:254, and where b is greater than or equal to a + 14.	R13979, R17378, R40039, R42616, R42616, R40039, R56257, R56346, H05467, H07018, R86778, H99527, H99526, H99763, N24571, N25539, N25635, N28490, N30121, N34013, N34136, N34233, N35730, N49189, N50244, N92737, W20356, AA255602, AA262707, AA255576, AA262183, AA279758, AA570002, AA572777, AA721016, AA814424, AA864521, AA902860, AA948310, A1024777, A1056401
829349	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 640 of SEQ ID NO:255, b is an integer of 15 to 654, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:255, and where b is greater than or equal to a + 14.	T39288, T47082, T50451, T50586, T59000, T59073, T59535, T59586, T63704, T63861, T69920, T69974, T71240, T72474, T72943, T90268, T90710, T83786, T95048, R31368, R33435, R34369, R34489, R73911, R80467, R80667, R94351, R97310, R97345, H57329, H57376, H62783, H64845, H65444, H82981, H83214, H93955, H93956, N29780, N42940, N45379, N57200, N80805, W06876, W15396, W47162, W47283, W52164, W52024, W52758, W73045, W73275, W73604, W73643, W86783, W87274, AA009954, AA010849, AA011288, AA022621, AA022757, AA025805, AA025929, AA025968, AA046835, AA054475, AA058513, AA063327, AA075215, AA075451, AA088739, AA088740, AA099371, AA099457, AA112397, AA113053, AA121065, AA121066, AA132025, AA132147, AA132237, AA132357, AA146935,

		AA147721, AA147756, AA147602, AA148113, AA156063, AA157120, AA157223, AA157610, AA165107, AA164710, AA173741, AA173185, AA187331, AA187332, AA187293, AA187393, AA187741, AA188097, AA187033, AA188455, AA188457, AA188467, AA216356, AA228668, AA229001, AA228993, AA229108, AA397406, AA482922, AA483319, AA483431, AA491567, AA501502, AA507889, AA508445, AA513947, AA515053, AA522563, AA523140, AA525478, AA524922, AA526106, AA534088, AA535846, AA548219, AA552477, AA555012, AA558315, AA564882, AA565458, F16817, F16991, F17527, AA582793, AA587225, AA588487, AA595626, AA602055, AA602240, AA603392, AA631634, AA638971, AA639988, AA640535, AA576051, AA576894, AA566049, AA655021, AA659001, AA661609, AA662354, AA664631, AA664721, AA664980, AA665338, AA688035, AA714993, AA715012, AA720861, AA730373, AA730633, AA742678, AA742934, AA746812, AA747153, AA747192, AA747959, AA808437, AA836880, AA837645, AA838637, AA872341, AA876822, AA922665, AA961515, AA968734, AA970649, AA978219, AA988051, AA988404, AA991418, AA994111, A1002489, A1053409, A1053609, A1053760, A1082351, A1083631, N83854, N83948, N85971, N86260, N86628, N87758, AA641679, AA642097, AA642839, C20758, AA092159, AA092465, AA094493
829354	<p>Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1978 of SEQ ID NO:256, b is an integer of 15 to 1992, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:256, and where b is greater than or equal to a + 14.</p>	
829388	<p>Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2259 of SEQ ID NO:257, b is an integer of 15 to 2273, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:257, and where b is greater than or equal to a + 14.</p>	
829540	<p>Preferably excluded from the present invention are</p>	N26408, N28830, N28838, N31522,

	one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1490 of SEQ ID NO:258, b is an integer of 15 to 1504, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:258, and where b is greater than or equal to a + 14.	W15157, W81560, W81561, AA126749, AA126756, AA126772, AA187148
829626	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1778 of SEQ ID NO:259, b is an integer of 15 to 1792, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:259, and where b is greater than or equal to a + 14.	
829730	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2034 of SEQ ID NO:260, b is an integer of 15 to 2048, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:260, and where b is greater than or equal to a + 14.	
829892	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1268 of SEQ ID NO:261, b is an integer of 15 to 1282, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:261, and where b is greater than or equal to a + 14.	R84306, N99830, N90467, AA113938, AA192541, AA243317, L44546, AA713588
829933	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 585 of SEQ ID NO:262, b is an integer of 15 to 599, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:262, and where b is greater than or equal to a + 14.	AA121059, AA429187
829938	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1247 of SEQ ID NO:263, b is an integer of 15 to 1261, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:263, and where b is greater than or equal to a + 14.	AA001837, AA142857, AA235114, AA235222, AA614412, AA687460, AA857702, AA857893, AA962131, AA962521
829969	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1006 of SEQ ID NO:264, b is an integer of 15 to 1020, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:264, and where b is greater than or equal to a + 14.	R22931, R23036, H09755, H47088, N38971, N38985, N57545, AA075344, AA075597, AA136299, AA136180, AA279124, AA279243, AA279928, AA279929, AA909786, A1000293, N48117, N48131
829982	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide	H40097, N80803, N93871, W07650, W15482, W40363, W42635, W45238,

	sequence described by the general formula of a-b, where a is any integer between 1 to 557 of SEQ ID NO:265, b is an integer of 15 to 571, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:265, and where b is greater than or equal to a + 14.	W67482, W67483, W70331, W72456, W73235, W73290, W76515, W78220, AA040927, AA040928, AA074829, AA075095, AA083686, AA166708, AA167049, AA228843, AA468686, AA469044, AA505509, AA548788, AA564157, AA595572, AA622149, AA633298, AA576799, AA746697, AA807946, AA873193, AA903706, AA919114, AA932502, AA938506, AA974058, AA977996, AI000750, N85073, N86741, N87037, N88197, N88746, AA090569
830007	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1336 of SEQ ID NO:266, b is an integer of 15 to 1350, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:266, and where b is greater than or equal to a + 14.	
830019	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1305 of SEQ ID NO:267, b is an integer of 15 to 1319, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:267, and where b is greater than or equal to a + 14.	T61424, T53868, T61391, T63785, R23153, R23154, R23905, R64468, R65575, R69390, R69523, R79153, R79154, H14532, H14533, H47318, H47402, H53647, H61347, H93017, H94242, N29789, N42932, W57927, W58148, W67701, W68160, W74342, W81702, W81703, W94692, W95218, W95440, W95785, AA043712, AA056570, AA114073, AA133633, AA133634, AA151774, AA149729, AA149782, AA149795, AA425861, AA425990, AA428095, AA428642, AA494401, AA515475, AA523534, AA548827, AA552032, AA564916, F16977, AA593645, AA613557, AA617694, AA618542, AA576565, AA576574, AA746168, AA766359, AA833956, AA837906, AA857421, AA857877, AA903383, AA903849, AA903888, AA916517, AA922889, AA962544, AA970534, AA974964, AA975402, AA976089, AA983583, AA992448, F18477, C04429, C17306
830073	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 3680 of SEQ ID NO:268, b is an integer of 15 to 3694, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:268, and where b is greater than or equal to a + 14.	T93694, T96159, H04182, H04181, H15428, H48586, N74976, W05676, W44928, AA085826, AA085971, AA126446, AA425304, AA425408, AA280817, AA280995, AA287270, AA287417, AA668788, AA836455, AA977754
830130	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1228 of SEQ ID	

	NO:269, b is an integer of 15 to 1242, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:269, and where b is greater than or equal to a + 14.	
830134	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2043 of SEQ ID NO:270, b is an integer of 15 to 2057, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:270, and where b is greater than or equal to a + 14.	
830135	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 946 of SEQ ID NO:271, b is an integer of 15 to 960, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:271, and where b is greater than or equal to a + 14.	
830148	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1153 of SEQ ID NO:272, b is an integer of 15 to 1167, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:272, and where b is greater than or equal to a + 14.	R15244, R31943, R31992, H06853, H06894, H13355, H30882, R84410, R84411, R94120, H53381, H97695, H99925, N46996, N69023, N77897, W00690, W19694, W38937, W74721, W74795, N89822, N89950, AA009490, AA009904, AA031349, AA031350, AA035629, AA035719, AA046140, AA062845, AA062905, AA079564, AA079636, AA116062, AA116046, AA126968, AA148568, AA159591, AA160429, AA161272, AA161273, AA160576, AA179774, AA180491, AA179635, AA182631, AA182727, AA179634, AA192371, AA192282, AA199831, AA251312, AA256883, AA255477, AA430121, AA533720, AA551694, AA552307, AA552661, AA582138, AA586611, AA587906, AA594387, AA602977, AA605299, AA633388, AA573941, AA574038, AA579715, AA687647, AA741352, AA838339, AA857603, AA858082, AA866081, AA865003, AA875861, AA910672, AA927563, A1076918, W21962
830149	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2757 of SEQ ID NO:273, b is an integer of 15 to 2771, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:273, and where b is greater than or equal to a + 14.	R60249, R60762, R63751, R67526, H95029, H95095, N59347, N77158, W19778, AA047615, AA047555, AA047687, AA047738, AA056453, AA070880, AA112293, AA113105, AA112550, AA112614, AA158015, AA158228, AA160995, AA160996, AA190555, AA191131, AA224574, AA227422, AA255563, AA255586, AA418477, AA424689, AA470392, AA515485, AA515507, AA583475,



		AA588210, AA602533, AA573902, AA568354, AA746111, AA766146, AA804893, N83302
830154	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1875 of SEQ ID NO:274, b is an integer of 15 to 1889, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:274, and where b is greater than or equal to a + 14.	
830183	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 590 of SEQ ID NO:275, b is an integer of 15 to 604, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:275, and where b is greater than or equal to a + 14.	
830194	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1367 of SEQ ID NO:276, b is an integer of 15 to 1381, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:276, and where b is greater than or equal to a + 14.	T51023, T51115, T52795, T53595, T56300, T56767, T59691, T59827, T59904, T63354, T72200, T72269, T92900, T92990, R07165, R07217, R44334, R49609, R44334, R49609, H11106, H20800, H22618, H42472, H43453, H50320, H50321, H69947, N20118, N21306, N26128, N63140, N67225, N67232, W45407, W56419, W56420, W72419, W76279, W94626, W94710, AA029459, AA029524, AA034511, AA035053, AA035563, AA039819, AA041465, AA053002, AA055974, AA056002, AA070356, AA070320, AA074029, AA074039, AA074189, AA074336, AA075645, AA075646, AA076380, AA084435, AA084465, AA084453, AA085290, AA086454, AA099172, AA101922, AA101959, AA099618, AA102011, AA112794, AA126226, AA126304, AA128510, AA129955, AA133875, AA128443, AA133328, AA133403, AA134003, AA130990, AA131028, AA132940, AA135158, AA135628, AA143273, AA146730, AA151853, AA155641, AA155696, AA155726, AA157967, AA158903, AA158902, AA158943, AA158944, AA159293, AA159526, AA161206, AA160558, AA160739, AA160740, AA165357, AA167787, AA169218, AA169512, AA169691, AA176365, AA179272, AA179388, AA180903, AA181001, AA181325, AA181508, AA182781, AA173899, AA187757, AA188120, AA186725, AA187070, AA187152, AA190896, AA199819, AA223210,

		AA223254, AA227038, AA232399, AA233288, AA243192, AA252285, AA492525, AA420611, AA420688, AA492171, AA492254, AA503950, AA507398, AA513704, AA513757, AA515944, AA525799, AA558212, AA563863, AA565107, F17110, AA582829, AA586678, AA603895, AA604163, AA568617, AA617883, AA622814, AA635987, AA569079, AA570078, AA570258, AA570419, AA573205, AA573965, AA574048, AA566065, AA748781, AA834135, AA837022, AA838454, AA838636, AA838049, AA838058, AA856831, AA909853, AA910298, AA927706, AA932101, AA937900, AA953604, AA969555, AA973234, AA978074, AA985430, AA985432, AA988742, AA994207, A1002611, A1014411, N84537, N85082, W22113, W22114, W22431, W22639, W23207, W23271, W29046, N88675, AA640915, AA092777
830207	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1135 of SEQ ID NO:277, b is an integer of 15 to 1149, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:277, and where b is greater than or equal to a + 14.	R51744, R88177, W05323, AA746479, AA761644, AA826038, W27619, AA642452
830242	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 797 of SEQ ID NO:278, b is an integer of 15 to 811, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:278, and where b is greater than or equal to a + 14.	
830328	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1246 of SEQ ID NO:279, b is an integer of 15 to 1260, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:279, and where b is greater than or equal to a + 14.	
830340	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1654 of SEQ ID NO:280, b is an integer of 15 to 1668, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:280, and where b is greater than or equal to a + 14.	
830341	Preferably excluded from the present invention are	T62985, T63236, T71911, T66677,

	one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2314 of SEQ ID NO:281, b is an integer of 15 to 2328, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:281, and where b is greater than or equal to a + 14.	T66678, T80777, T81178, R16218, R16219, R67281, H15642, H15643, R96139, R96356, H61487, H61952, H62021, H62022, H62510, H62577, H62887, H63016, H65659, H65660, H72388, H72834, H80906, H97768, N30162, N35776, N52509, N66853, W44421, AA004323, AA004410, AA025214, AA026003, AA040205, AA040849, AA079158, AA079159, AA137066, AA137080, AA137137, AA136971, AA193479, AA532656, AA602312, AA828635, AA872751, AA934418, D80729, C15337
830351	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 942 of SEQ ID NO:282, b is an integer of 15 to 956, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:282, and where b is greater than or equal to a + 14.	
830358	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1388 of SEQ ID NO:283, b is an integer of 15 to 1402, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:283, and where b is greater than or equal to a + 14.	
830390	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 661 of SEQ ID NO:284, b is an integer of 15 to 675, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:284, and where b is greater than or equal to a + 14.	
830400	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1325 of SEQ ID NO:285, b is an integer of 15 to 1339, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:285, and where b is greater than or equal to a + 14.	T40239, T41103, T60782, T61153, T92326, T95403, R16530, R16587, R46049, R49231, R49231, R46049, H26122, H26387, H67872, H67872, H97917, N23194, N29748, N57652, N64158, N67587, N77509, N80178, W03502, W23838, W57929, W72584, AA011087, AA011088, AA070667, AA074878, AA075068, AA075019, AA076166, AA079857, AA082235, AA099016, AA099093, AA100754, AA113152, AA126886, AA128207, AA126932, AA128546, AA130882, AA136302, AA136408, AA143052, AA143693, AA148079, AA149931, AA151001, AA151091, AA155761, AA157290, AA160781, AA165535, AA173281, AA179903, AA180211, AA181162, AA181673, AA181986,

		AA187551, AA191657, AA192202, AA196746, AA196944, AA223166, AA224485, AA242866, AA397377, AA468734, AA514807, AA523669, AA534165, AA534195, AA565551, AA565552, H67199, AA581627, AA588734, AA588752, AA593857, AA595407, AA595555, AA603965, AA610486, AA614617, AA631563, AA635960, AA636057, AA576256, AA577470, AA580124, AA580480, AA714208, AA728790, AA729276, AA729361, AA744895, AA745002, AA746940, AA746948, AA747346, AA804602, AA810873, AA833970, AA836938, AA838563, AA858405, AA872330, AA922975, AA946823, AA954185, AA962678, AA978008, AA985504, AA987717, AI004904, AI017374, AI075264, F19611, AI089951, N83301, AA082282, AA091465, AA093298, AA094459
830437	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1384 of SEQ ID NO:286, b is an integer of 15 to 1398, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:286, and where b is greater than or equal to a + 14.	
830458	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 912 of SEQ ID NO:287, b is an integer of 15 to 926, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:287, and where b is greater than or equal to a + 14.	T47583, T47584, T49761, T50148, T50203, T47161, R11382, R14878, H18220, H18258, R92715, N78687, W20222, W58210, W58319, W72115, W77801, W79332, W79431, W79487, W79631, W94437, N90582, AA043441, AA043442, AA148009, AA147947, AA150837, AA224863, AA225964, AA226110, AA259194, AA259193, AA420769, AA420829, AA470787, AA493672, AA501962, AA502082, AA506908, AA528607, AA588435, AA603500, AA603814, AA627229, AA627233, AA627240, AA632058, AA632689, AA639239, AA579023, AA580698, AA662633, AA661967, AA665215, AA729443, AA730546, AA737851, AA745424, AA745526, AA747036, AA878568, AA879157, AA886627, AA902180, AA922294, AA933050, AA962580, AA977360, AA985679, AA996058, AA996145, AI053546, AI085892, N83274, W15194, N88934, C04128, AA640839, AA091328, AA093116, AA094048, AA094287
830466	Preferably excluded from the present invention are	

	one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 3080 of SEQ ID NO:288, b is an integer of 15 to 3094, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:288, and where b is greater than or equal to a + 14.	
830497	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1969 of SEQ ID NO:289, b is an integer of 15 to 1983, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:289, and where b is greater than or equal to a + 14.	T47088, T47089, T58430, T58462, R00971, H42144, N77388, W51953, W52502, AA036671, AA114976, AA593693, AA575857, C01052
830511	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1284 of SEQ ID NO:290, b is an integer of 15 to 1298, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:290, and where b is greater than or equal to a + 14.	
830512	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2445 of SEQ ID NO:291, b is an integer of 15 to 2459, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:291, and where b is greater than or equal to a + 14.	
830513	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 556 of SEQ ID NO:292, b is an integer of 15 to 570, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:292, and where b is greater than or equal to a + 14.	
830540	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2454 of SEQ ID NO:293, b is an integer of 15 to 2468, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:293, and where b is greater than or equal to a + 14.	T66458, T98908, R15832, R21916, R22565, H12306, R99043, H57499, H82961, AA046203, AA046283, AA055081, AA055141, AA173411, AA173467, AA173996, AA176693
830550	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1066 of SEQ ID NO:294, b is an integer of 15 to 1080, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:294, and where b is greater than or equal to a + 14.	R50040, R60172, R71512, H09125, H09475, H21789, R84538, R85928, R94762, R96633, R96680, R97580, H53135, H53241, H82960, H83191, N68166, N68684, N77903, N80174, N80625, N92442, N93242, N93314, N98261, W03498, W05839, W20000, W25100, W31279, W37087, W60751, W67554, W67583, W73877, W77814, W80412, W95868, W95954, N91343,

		AA026891, AA026892, AA033547, AA034170, AA069175, AA088435, AA151307, AA161037, AA237097, AA251326, AA251729, AA428848, AA429940, AA287366, AA287504, AA470593, AA470594, AA514493, AA564438, H67293, AA582501, AA583172, AA587111, AA602517, AA603483, AA569955, AA732412, AA737913, AA810504, AA832193, AA857743, AA915872, AA915896, AA915992, AA948498, AA983538, AA991546, AI052409, AI053921
830567	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2681 of SEQ ID NO:295, b is an integer of 15 to 2695, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:295, and where b is greater than or equal to a + 14.	R69708, R75813, R75814, N22294, N47088, N50300, N50983, N81194, N93236, AA074258, AA083867, AA083973, AA195801, AA196063, AA252500, AA252415, AA258014, AA287593, AA291332, AA492017, AA522597, AA617684, AA713960, AA740158, AA749386, AA808100, AA808680, AA814350, AA826203, AA831453, AA887306, AA918645, AA972761, N88184
830586	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1380 of SEQ ID NO:296, b is an integer of 15 to 1394, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:296, and where b is greater than or equal to a + 14.	R99131, H81094, W01508, AA045861, AA085947, AA102188, AA146772, AA148854, AA233843, AA424679, AA491204, AA514459, AA532818, AA809984, AA838521, AA954880, AI089939
830632	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 984 of SEQ ID NO:297, b is an integer of 15 to 998, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:297, and where b is greater than or equal to a + 14.	T47818, R21519, R21621, R22056, R22112, R31393, R32890, R48823, R48824, R66656, R67377, R71682, H25037, H25038, H25842, H26215, H26515, H26994, H28312, H28313, H29756, H30178, H41920, H41966, H42490, H43473, R83733, R85464, R88798, R89058, R93321, H52733, H59363, H60020, H73314, H73513, H80831, H80832, H82603, H86794, H86795, H86853, H86852, H92710, H96832, H98741, N23451, N23463, N26478, N26861, N31350, N31593, N35529, N39970, N42652, N62104, N74283, N76446, N78334, N92771, W04383, W19424, W20392, W24569, W35168, W60060, W60111, W84373, W84420, AA025658, AA029558, AA062705, AA062707, AA063390, AA062771, AA081934, AA126557, AA136019, AA151638, AA192245, AA194655, AA470430, AA493634, AA552261, AA552348, AA565278, AA565462, AA583788, AA593646, AA594277, AA604853, AA613755.

		AA632449, AA632505, AA657974, AA730677, AA730804, AA748100, AA765824, AA857805, AA954102, AA961763, AA962500, AA974525, AA983564, AA987422, AA987934, AA989423, A1000235, F19140, N84058, N84994, C03222, AA091370, AA091545
830645	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1652 of SEQ ID NO:298, b is an integer of 15 to 1666, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:298, and where b is greater than or equal to a + 14.	
830652	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2430 of SEQ ID NO:299, b is an integer of 15 to 2444, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:299, and where b is greater than or equal to a + 14.	
830659	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1012 of SEQ ID NO:300, b is an integer of 15 to 1026, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:300, and where b is greater than or equal to a + 14.	T65101, T66494, T66636, T84051, T86086, R05580, R13805, R15868, R16050, H05221, H05222, H13512, H16069, H18275, H21247, H44169, R83705, R92365, H48479, H48643, H54436, H54526, H73472, H73726, H97495, N29822, N30479, N31551, N32563, N39176, N39961, N45251, N68667, N91684, W07693, W32510, W32607, W38017, W74179, W79849, AA018138, AA028191, AA033572, AA033571, AA042915, AA043002, AA053878, AA054501, AA058344, AA099556, AA101993, AA134643, AA143525, AA176419, AA424269, AA555196, AA769107, AA987653, A1076212, N84624, N85006, A1084132, A1084154, AA094327
830696	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 816 of SEQ ID NO:301, b is an integer of 15 to 830, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:301, and where b is greater than or equal to a + 14.	
830706	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 3286 of SEQ ID NO:302, b is an integer of 15 to 3300, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:302, and where b is	

	greater than or equal to $a + 14$ .	
830743	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 461 of SEQ ID NO:303, b is an integer of 15 to 475, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:303, and where b is greater than or equal to $a + 14$ .	N30323, N56655, N69079, N69946, N80244, N98327, W07371, W42660, W45185, W55989, W56279, W68387, W68503, W72685, W74708, W74677, W77791, W80647, AA010723, AA011171, AA033537, AA034221, AA035773, AA056334, AA062820, AA132021, AA132124, AA135594, AA135681, AA151293, AA151292, AA181331, AA186392, AA187084, AA228662, AA228680, AA229819, AA468802, AA470869, AA483684, AA491891, AA514852, AA533423, AA548946, AA563674, AA564612, AA594511, AA600707, AA622053, AA635767, AA639353, AA662887, AA664589, AA729365, AA747035, AA747774, AA814124, AA873167, AA886626, AA903495, AA903981, AA922807, AA969768, AA973174, AA974282, AA976458, AA977143, AA983332, A1025140, A1066527, F19035, F19464, C03984, C13986, C14221, C14299, C14336, C14341, C14380, C14385, C14396, C14434, C14483, C14504, C14513, C15788
830770	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2888 of SEQ ID NO:304, b is an integer of 15 to 2902, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:304, and where b is greater than or equal to $a + 14$ .	
830830	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1539 of SEQ ID NO:305, b is an integer of 15 to 1553, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:305, and where b is greater than or equal to $a + 14$ .	
830838	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1973 of SEQ ID NO:306, b is an integer of 15 to 1987, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:306, and where b is greater than or equal to $a + 14$ .	
830851	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 771 of SEQ ID NO:307, b is an integer of 15 to 785, where both a and b correspond to the positions of nucleotide	



	residues shown in SEQ ID NO:307, and where b is greater than or equal to a + 14.	
830853	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2164 of SEQ ID NO:308, b is an integer of 15 to 2178, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:308, and where b is greater than or equal to a + 14.	
830856	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 861 of SEQ ID NO:309, b is an integer of 15 to 875, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:309, and where b is greater than or equal to a + 14.	
830862	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 742 of SEQ ID NO:310, b is an integer of 15 to 756, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:310, and where b is greater than or equal to a + 14.	T46908, T46909, T46921, T46922, T50921, T52918, T53038, T56001, T59028, T94115, T94204, R53898, R53908, H02747, H27523, H77792, H88026, H88248, H90255, H96065, H88248, N21994, N64072, N73723, N74262, N75815, N77939, W03894, W23887, AA081082, AA113423, AA115852, AA143290, AA143335, AA146868, AA157054, AA157208, AA179118, AA187792, AA188385, AA468513, AA468983, AA501970, AA523481, AA528461, AA533759, AA533618, AA535287, AA541570, AA558529, L44430, AA604961, AA568927, AA659814, AA661481, AA661996, AA731036, AA748135, AA847331, AA878667, AA885549, AA935403, AA938035, A1001062, F19242, N83489, N83646, N84328, N85002, N85167, N85223, N85325, N85833, N85949, N86287, N86329, N87923, N83150, AA642852, AA091775, AA093919
830879	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 837 of SEQ ID NO:311, b is an integer of 15 to 851, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:311, and where b is greater than or equal to a + 14.	T62074, T62130, T67747, T67857, R44816, R48904, R44816, H13822, H29311, W37451, N90567, AA128266, AA164552, AA235044, AA236012, AA746229, AA962194, AA987868, AA994828, A1000188, A1015557
830919	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1321 of SEQ ID NO:312, b is an integer of 15 to 1335, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:312, and where b is	

	greater than or equal to $a + 14$ .	
830969	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 502 of SEQ ID NO:313, b is an integer of 15 to 516, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:313, and where b is greater than or equal to $a + 14$ .	
830991	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1819 of SEQ ID NO:314, b is an integer of 15 to 1833, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:314, and where b is greater than or equal to $a + 14$ .	
831002	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1340 of SEQ ID NO:315, b is an integer of 15 to 1354, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:315, and where b is greater than or equal to $a + 14$ .	
831003	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2407 of SEQ ID NO:316, b is an integer of 15 to 2421, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:316, and where b is greater than or equal to $a + 14$ .	T64373, N48387, W52748, W52754, W70187, AA029541, AA034463, AA058497, AA082001, AA082284, AA085967, AA088397, AA133444, AA133477, AA149568, AA187408, AA226818, AA226855
831021	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1078 of SEQ ID NO:317, b is an integer of 15 to 1092, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:317, and where b is greater than or equal to $a + 14$ .	
831036	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1366 of SEQ ID NO:318, b is an integer of 15 to 1380, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:318, and where b is greater than or equal to $a + 14$ .	
831071	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2598 of SEQ ID NO:319, b is an integer of 15 to 2612, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:319, and where b is greater than or equal to $a + 14$ .	

831094	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 929 of SEQ ID NO:320, b is an integer of 15 to 943, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:320, and where b is greater than or equal to a + 14.	
831099	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2945 of SEQ ID NO:321, b is an integer of 15 to 2959, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:321, and where b is greater than or equal to a + 14.	<p>T58120, T90056, T90158, T94290, T94639, R69200, R69590, R69678, R76031, H65424, H65425, N32273, N40465, N47619, N48504, N66482, N67212, N67243, N67881, N71915, N72302, N92538, N94512, W03004, W06930, W20370, W23962, W38380, W38525, W38716, W39486, W42582, W42594, W44824, W48665, W51898, W52474, W53040, W60142, N90075, N90423, AA025009, AA024962, AA029382, AA029726, AA031500, AA031546, AA037283, AA037749, AA039259, AA044145, AA044261, AA065061, AA070027, AA082386, AA083544, AA083757, AA088692, AA088829, AA099577, AA100236, AA100245, AA100517, AA112739, AA112091, AA116055, AA130509, AA130510, AA132145, AA135909, AA136308, AA136413, AA136528, AA136751, AA146853, AA146852, AA148049, AA156943, AA159808, AA165022, AA173867, AA181803, AA182563, AA182776, AA186553, AA186858, AA192463, AA194658, AA255837, AA261995, AA423999, AA493599, AA228337, AA228348, AA506755, AA506420, AA513968, AA514542, AA522900, AA524125, AA551485, AA553912, AA563900, AA594966, AA602651, AA610339, AA610361, AA614772, AA618333, AA576828, AA665045, AA714493, AA729997, AA738153, AA768641, AA804931, AA806122, AA827914, AA857664, AA876216, AA877173, AA877646, AA894385, AA922728, AA947835, AA977110, AA984009, AA988275, AA988567, N84005, N84600, N84939, N85553, AI084028, N86141, N88049, N89450, N89451, C02877, C02980, C03631, C05243, C05332, C05993, AA642453, AA090838, AA089614, AA091652, AA093130, AA093851</p>
831113	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b,	AA122085, AA147371, AI005336

	where a is any integer between 1 to 788 of SEQ ID NO:322, b is an integer of 15 to 802, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:322, and where b is greater than or equal to a + 14.	
831120	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1710 of SEQ ID NO:323, b is an integer of 15 to 1724, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:323, and where b is greater than or equal to a + 14.	
831172	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2247 of SEQ ID NO:324, b is an integer of 15 to 2261, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:324, and where b is greater than or equal to a + 14.	
831178	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1199 of SEQ ID NO:325, b is an integer of 15 to 1213, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:325, and where b is greater than or equal to a + 14.	
831184	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2750 of SEQ ID NO:326, b is an integer of 15 to 2764, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:326, and where b is greater than or equal to a + 14.	
831203	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1750 of SEQ ID NO:327, b is an integer of 15 to 1764, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:327, and where b is greater than or equal to a + 14.	
831210	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 557 of SEQ ID NO:328, b is an integer of 15 to 571, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:328, and where b is greater than or equal to a + 14.	AA057014, AA059289
831228	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 459 of SEQ ID	

	NO:329, b is an integer of 15 to 473, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:329, and where b is greater than or equal to a + 14.	
831256	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1321 of SEQ ID NO:330, b is an integer of 15 to 1335, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:330, and where b is greater than or equal to a + 14.	R17500, R48877, H12160, R84358, H90367, N33987, AA161057
831257	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1032 of SEQ ID NO:331, b is an integer of 15 to 1046, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:331, and where b is greater than or equal to a + 14.	T49922, T85470, R37545, H03610, AA005184, AA045346
831277	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1297 of SEQ ID NO:332, b is an integer of 15 to 1311, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:332, and where b is greater than or equal to a + 14.	
831317	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1430 of SEQ ID NO:333, b is an integer of 15 to 1444, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:333, and where b is greater than or equal to a + 14.	T39850, T47708, T47709, T47863, T51491, T52507, T53819, T53951, T55884, T60330, T60359, T60364, T60380, T60480, T60634, T61198, T61280, T61878, T62028, T67704, T67742, T67780, T67853, T67910, T68010, T68058, T68132, T68154, T68379, T68998, T68999, T69078, T69079, T69119, T69177, T69442, T70496, T71707, T72285, T72505, T72998, T73123, T73679, T73756, T73761, T73837, T74031, T74383, T74405, T74655, T74784, T74798, T74892, T85320, T85533, R83453, R88738, R90989, R90995, H58528, H59441, H60092, H60282, H60589, H67401, H67458, H72811, H79422, H80518, H80570, H91775, H91816, N57814, W60714, W60741, AA034367, AA040550, AA040667, AA242768, AA424551, AA424642, R29495, R29660, R29089, C21224
831339	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1016 of SEQ ID NO:334, b is an integer of 15 to 1030, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:334, and where b is	

	greater than or equal to $a + 14$ .	
831363	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2113 of SEQ ID NO:335, b is an integer of 15 to 2127, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:335, and where b is greater than or equal to $a + 14$ .	T58736, T58803, T61766, T64470, T64610, T67816, T68878, T68952, T72450, T72511, T72968, T73613, T73939, H41914, H41957, N75040, W05718, AA043436, AA043416, AA045231, AA058807, AA484773, AA502762, AA503811, AA527553, AA744171, AA902935, AA903099, A1002033
831367	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 833 of SEQ ID NO:336, b is an integer of 15 to 847, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:336, and where b is greater than or equal to $a + 14$ .	
831379	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 688 of SEQ ID NO:337, b is an integer of 15 to 702, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:337, and where b is greater than or equal to $a + 14$ .	R26001, R26804, R82629, R82630, H21598, H27310, H27309, H38082, H38083, H44451, H44494, H47613, R83356, R83791, R96066, R96103, H72512, H72910, H80449, H80450, H90511, H90607, N71766, N94349, W16956, W23496, W24351, W46455, W46523, W48658, W70263, W73002, W76239, W92963, W92964, AA157329, AA157426, AA458665, AA229554, AA280810, AA280936, AA490898, AA491084, AA493730, AA527336, AA534762, AA535794, F17720, AA603439, AA568655, AA659071, AA826699, AA872867, AA876999, AA932403, AA953149, AA953343, A1000023, A1017353, A1094807, N95548, C02063, C04109
831385	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 861 of SEQ ID NO:338, b is an integer of 15 to 875, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:338, and where b is greater than or equal to $a + 14$ .	
831390	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1434 of SEQ ID NO:339, b is an integer of 15 to 1448, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:339, and where b is greater than or equal to $a + 14$ .	T53890, T54037, T81546, T81973, R20470, R21066, R45288, R46246, R45288, R46246, H13340, H17537, H30523, R85229, R85230, R94643, R94685, R94686, H52010, H52125, H71328, H71376, N25973, N28794, N30891, N36603, N41703, N62205, N63213, N76503, W45706, W44353, W52126, W74523, W79862, AA033566, AA034468, AA099015, AA099092, AA100315, AA129588, AA167137, AA194961, AA226935, AA226943, AA418898, AA428909,

		AA485083, AA485195, AA505107, AA506087, AA516109, AA525370, AA617946, AA627402, AA573848, AA574063, AA809830, AA834509, AA837985, AA862394, AA862989, AA974789, AA988779, AI000171, AI094917, W24010, N88026, C20972
831391	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 829 of SEQ ID NO:340, b is an integer of 15 to 843, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:340, and where b is greater than or equal to a + 14.	
831405	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1279 of SEQ ID NO:341, b is an integer of 15 to 1293, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:341, and where b is greater than or equal to a + 14.	T54632, T54714, T55384, T55812, T56220, T60613, T69578, R08164, R08219, T78003, T78164, R01577, R12676, R16414, H60551, N21984, N25878, N25887, N75352, W01648, W72541, W76166, W86984, W86811, W88909, W88788, AA022691, AA022784, AA193302, AA194256, AA235873, AA425660, AA573463, AA953249, R29055
831442	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1259 of SEQ ID NO:342, b is an integer of 15 to 1273, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:342, and where b is greater than or equal to a + 14.	
831476	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1779 of SEQ ID NO:343, b is an integer of 15 to 1793, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:343, and where b is greater than or equal to a + 14.	R48303, R48405, R73778, H30456, H81254, W02773, W24831, W73089, W73194, AA034015, AA151153, AA151154, AA418429, AA424672, AA593592, AA910532, AA987246, AI001017, C02335, C04320
831488	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1658 of SEQ ID NO:344, b is an integer of 15 to 1672, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:344, and where b is greater than or equal to a + 14.	
831518	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2095 of SEQ ID NO:345, b is an integer of 15 to 2109, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:345, and where b is greater than or equal to a + 14.	

831519	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1700 of SEQ ID NO:346, b is an integer of 15 to 1714, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:346, and where b is greater than or equal to a + 14.	
831521	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1658 of SEQ ID NO:347, b is an integer of 15 to 1672, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:347, and where b is greater than or equal to a + 14.	
831550	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1469 of SEQ ID NO:348, b is an integer of 15 to 1483, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:348, and where b is greater than or equal to a + 14.	
831560	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1828 of SEQ ID NO:349, b is an integer of 15 to 1842, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:349, and where b is greater than or equal to a + 14.	T56438, R22852, R46063, R52365, R81781, R81879, H02958, H04256, H05743, H05849, H23235, H23349, H43210, H43260, H87699, H91571, W00708, W56717, W56762, W70251, W70252, AA026841, AA027043, AA041261, AA041495, AA043451, AA043452, AA054505, AA054366, AA055050, AA055129, AA147629, AA147667
831562	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2994 of SEQ ID NO:350, b is an integer of 15 to 3008, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:350, and where b is greater than or equal to a + 14.	
831570	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2742 of SEQ ID NO:351, b is an integer of 15 to 2756, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:351, and where b is greater than or equal to a + 14.	
831593	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1631 of SEQ ID NO:352, b is an integer of 15 to 1645, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:352, and where b is	



	greater than or equal to $a + 14$ .	
831596	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1623 of SEQ ID NO:353, b is an integer of 15 to 1637, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:353, and where b is greater than or equal to $a + 14$ .	
831627	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1105 of SEQ ID NO:354, b is an integer of 15 to 1119, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:354, and where b is greater than or equal to $a + 14$ .	AA147578, AA156449, AA588796, AA863066, D80116
831649	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 724 of SEQ ID NO:355, b is an integer of 15 to 738, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:355, and where b is greater than or equal to $a + 14$ .	R21047
831664	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1952 of SEQ ID NO:356, b is an integer of 15 to 1966, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:356, and where b is greater than or equal to $a + 14$ .	R35205, H13039, R84255, W24589, W93157, AA186436, AA188774, AA227246, AA658889, AA838204, W22056, W25833, W28198, W28494, AA090436, AA089530, AA089667
831674	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1548 of SEQ ID NO:357, b is an integer of 15 to 1562, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:357, and where b is greater than or equal to $a + 14$ .	
831684	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1917 of SEQ ID NO:358, b is an integer of 15 to 1931, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:358, and where b is greater than or equal to $a + 14$ .	T64083, R54664, R54665, W52888, W60096, W60162, AA009843, AA009870, AA236225, AA236291, AA459452, AA465675, AA554776, AA563899, AA583755, AA593849, AA596013, AA627978, AA573921, AA747840, AA828086, AA830260, AA837593, AA996154, C01662
831687	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 855 of SEQ ID NO:359, b is an integer of 15 to 869, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:359, and where b is greater than or equal to $a + 14$ .	T49489, R05976, R55046, N21648, N31054, N48001, AA464953, AA426224, AA430556, AA600829, AA744708, AA747361, AA976473, A1097658

831726	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 547 of SEQ ID NO:360, b is an integer of 15 to 561, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:360, and where b is greater than or equal to a + 14.	
831736	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1666 of SEQ ID NO:361, b is an integer of 15 to 1680, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:361, and where b is greater than or equal to a + 14.	T60384, T93026, T83297, R17403, R17423, R21319, H65765, N94506, W23956, W24344, W45068, W57786, W57860, W81343, AA058929, AA151788, AA151833
831762	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 726 of SEQ ID NO:362, b is an integer of 15 to 740, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:362, and where b is greater than or equal to a + 14.	
831801	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1310 of SEQ ID NO:363, b is an integer of 15 to 1324, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:363, and where b is greater than or equal to a + 14.	T39530, T64430, R36089, H12597, H12647, H19534, H20096, H26648, H26663, W15192, W45569, W45621, AA018144, AA018145, AA018470, AA039510, AA039529, AA047549, AA047837, AA057785, AA074201, AA075686, AA079138, AA135599, AA135658, AA147502, AA147931, AA156715, AA156811, AA188215, AA186362, AA425996, AA283917, AA514670, AA522463, AA714301, AA742700, AA872728, AA887841, AA971644, A1015637, A1053971, A1054233, A1074507, A1084901, W28363
831848	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2839 of SEQ ID NO:364, b is an integer of 15 to 2853, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:364, and where b is greater than or equal to a + 14.	T77112, R13655, R19353, R19511, R24780, R35812, R36752, R38177, R43861, R44629, R45511, R43861, R45511, R44629, R71248, R71299, R82784, H00629, H01917, H04479, H45706, H45757, H94039, H94125, N30574, N57220, AA033684, AA114107, AA253260, AA461547, AA460619, AA715125, A1096588, C03714, AA092127
831861	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1823 of SEQ ID NO:365, b is an integer of 15 to 1837, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:365, and where b is greater than or equal to a + 14.	T57456, T58038, T58104, R08156, R27046, R28341, R28340, N32411, N56831, N78961, W16984, W16954, W17352, W74522, W79861, AA025882, AA025883, AA084109, AA100121, AA100060, AA132713

831866	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1809 of SEQ ID NO:366, b is an integer of 15 to 1823, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:366, and where b is greater than or equal to a + 14.	
831878	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 884 of SEQ ID NO:367, b is an integer of 15 to 898, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:367, and where b is greater than or equal to a + 14.	
831899	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1103 of SEQ ID NO:368, b is an integer of 15 to 1117, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:368, and where b is greater than or equal to a + 14.	AA159048, AA768390, AA806956
831913	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2212 of SEQ ID NO:369, b is an integer of 15 to 2226, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:369, and where b is greater than or equal to a + 14.	
831972	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 3622 of SEQ ID NO:370, b is an integer of 15 to 3636, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:370, and where b is greater than or equal to a + 14.	
831985	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 4025 of SEQ ID NO:371, b is an integer of 15 to 4039, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:371, and where b is greater than or equal to a + 14.	
831986	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1585 of SEQ ID NO:372, b is an integer of 15 to 1599, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:372, and where b is greater than or equal to a + 14.	
832010	Preferably excluded from the present invention are	

	one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 450 of SEQ ID NO:373, b is an integer of 15 to 464, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:373, and where b is greater than or equal to a + 14.	
832016	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 876 of SEQ ID NO:374, b is an integer of 15 to 890, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:374, and where b is greater than or equal to a + 14.	
832041	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1860 of SEQ ID NO:375, b is an integer of 15 to 1874, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:375, and where b is greater than or equal to a + 14.	R63637, R92994, N30838, N30844, N41366, N41372, AA639771
832044	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2004 of SEQ ID NO:376, b is an integer of 15 to 2018, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:376, and where b is greater than or equal to a + 14.	T56668, R09616, R20197, R44983, R52998, R52997, R44983, H06485, H06543, H09799, H09885, H24790, N57987, N62197, N76494, W02915, W78217, AA041290, AA041323, AA074236, AA075127, AA075212, AA075847, AA088708, AA088793, AA112359, AA121803, AA151677, AA166711, AA167069, AA181608, AA188478, AA194067, AA194182, AA221025, AA221037, AA228036, AA228145, AA557397, AA564567, AA582681, AA582151, AA601549, AA613841, AA832393, AA846987, AA865356, AA866164, AA872667, AA862962, AA911092, AA937359, A1000072, D83877
832049	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 804 of SEQ ID NO:377, b is an integer of 15 to 818, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:377, and where b is greater than or equal to a + 14.	
832122	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2551 of SEQ ID NO:378, b is an integer of 15 to 2565, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:378, and where b is greater than or equal to a + 14.	
832148	Preferably excluded from the present invention are	T78202, R37864, R62706, R78737.

	one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1666 of SEQ ID NO:379, b is an integer of 15 to 1680, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:379, and where b is greater than or equal to a + 14.	R78736, H62109, N50394, N51659, N67973, N80394, W33108, W33107, AA016055, AA074831, AA075097, AA256793, AA256472, AA418825, AA418922, AA430755, AA280663, AA281049, AA467867, AA502148, H71558, AA721278, AA748880, AA809767, AA810852, AA832174, AA911263, AA938484, AA975282, D80672, D81573, D81746, A1096900, C02375
832197	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1253 of SEQ ID NO:380, b is an integer of 15 to 1267, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:380, and where b is greater than or equal to a + 14.	
832237	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1017 of SEQ ID NO:381, b is an integer of 15 to 1031, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:381, and where b is greater than or equal to a + 14.	R36943, R42259, R53230, R42259, H09607, AA150724, AA831055
832246	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1583 of SEQ ID NO:382, b is an integer of 15 to 1597, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:382, and where b is greater than or equal to a + 14.	H13698, H13750, R91283, R91322, H97506, N64810, N75659, W61290, W65386, H54890, AA568261, AA830860, AA863239, AA873329, AA938701, D82264, C18047
832256	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 161 of SEQ ID NO:383, b is an integer of 15 to 175, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:383, and where b is greater than or equal to a + 14.	
832280	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2157 of SEQ ID NO:384, b is an integer of 15 to 2171, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:384, and where b is greater than or equal to a + 14.	H09977, H09978, R89392, R94438, H93033, H93466, H93904, N29334, N53767, N57027, N71868, N71879, N73126, W24652, AA026682, AA047124, AA127259, AA224396, AA224473, AA227220, AA236734, AA236763, AA236910, AA236919
832285	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2350 of SEQ ID NO:385, b is an integer of 15 to 2364, where both a and b correspond to the positions of nucleotide	R12740, R14184, R15171, R26447, R28455, R34165, R35396, R39792, R40473, R49696, R41588, R40473, R49696, R70668, R70669, R79640, R79833, H02312, H08199, H08297, R99351, H84241, H84567, H85554.

	residues shown in SEQ ID NO:385. and where b is greater than or equal to a + 14.	N24354, N25230, N32462, N33863, N64676, N70374, N80109, W47526, W47527, W80678, W80934, W93668, AA082195, AA223758, AA243624, AA255527, AA256711, AA262387, AA281015, AA281094, AA281183, AA281203, AA287927, AA287991, AA505084, AA505086, AA525301, AA553559, AA564243, AA582189, AA737010, AA808271, AA872481, AA937541, A1015987, C01015, C20842
832294	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2850 of SEQ ID NO:386, b is an integer of 15 to 2864, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:386. and where b is greater than or equal to a + 14.	
832326	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2669 of SEQ ID NO:387, b is an integer of 15 to 2683, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:387, and where b is greater than or equal to a + 14.	
832333	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1432 of SEQ ID NO:388, b is an integer of 15 to 1446, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:388, and where b is greater than or equal to a + 14.	
832346	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 709 of SEQ ID NO:389, b is an integer of 15 to 723, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:389, and where b is greater than or equal to a + 14.	T88928, R12446, R37113, R42462, H15692, H18859, N34664, AA132220, AA224337, AA460720, AA492479
832370	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1032 of SEQ ID NO:390, b is an integer of 15 to 1046, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:390, and where b is greater than or equal to a + 14.	
832381	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 685 of SEQ ID NO:391, b is an integer of 15 to 699, where both a	

	and b correspond to the positions of nucleotide residues shown in SEQ ID NO:391, and where b is greater than or equal to a + 14.	
832394	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1531 of SEQ ID NO:392, b is an integer of 15 to 1545, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:392, and where b is greater than or equal to a + 14.	
832454	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 735 of SEQ ID NO:393, b is an integer of 15 to 749, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:393, and where b is greater than or equal to a + 14.	T57094, T58711, T68990, T71879, R92183, H93778, N63977, N80768, AA034382, AA034383, AA057664, AA235744, AA425865, AA524693, AA551804, AA523604, AA614639, AA740316, AA872373, AA938571, AA947337, R28997, AA640968, C21135
832465	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 597 of SEQ ID NO:394, b is an integer of 15 to 611, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:394, and where b is greater than or equal to a + 14.	R36004, R36378, H71881, H96279, N50049, N63692, W74426, W79180, W87805, AA421015, AA527679, AA833773, AA987375, F19351, AA642491, C14893, C14937
832475	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1842 of SEQ ID NO:395, b is an integer of 15 to 1856, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:395, and where b is greater than or equal to a + 14.	
832495	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2637 of SEQ ID NO:396, b is an integer of 15 to 2651, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:396, and where b is greater than or equal to a + 14.	
832498	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2493 of SEQ ID NO:397, b is an integer of 15 to 2507, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:397, and where b is greater than or equal to a + 14.	T67126, T67127, R13516, R20638, H64071, N22361, N25516, N39506, N75609, N78204, W40313, W45344, AA074739, AA074803, AA143509, AA523999, AA552542, AA554032, N20483, AA588804, AA617733, AA577150, AA577309, AA579423, AA740813, AA835721, AA836640, AA909766, AA936979, AA947310, N26815, A1085484, D78707, W67520, W68152
832501	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b.	

	where a is any integer between 1 to 1259 of SEQ ID NO:398, b is an integer of 15 to 1273, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:398, and where b is greater than or equal to a + 14.	
832505	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 3760 of SEQ ID NO:399, b is an integer of 15 to 3774, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:399, and where b is greater than or equal to a + 14.	T50501, T50636, T92136, R52390, R59648, H06170, H28886, H28885, R96577, R96600, H84171, H94122, H98228, N36866, N36872, N46136, N46142, N63589, N66323, W48779, W49798, AA029033, AA054487, AA058524, AA084466, AA086177, AA098967, AA099485, AA100345, AA147008, AA147009, AA146910, AA146909, AA160346, AA159865, AA192832, AA203513, AA252521, AA252553, AA463513, AA463570, AA421250, AA425704, AA427774, AA278328, AA278999, AA280712, AA281733, AA281871, AA282407, AA282626, AA283639, AA542810, AA557893, AA568486, AA569759, AA577522, AA659517, AA659737, AA664537, AA713950, AA805488, AA835999, AA876619, AA931568, AA935758, AA946722, A1000603, D82640
832539	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1508 of SEQ ID NO:400, b is an integer of 15 to 1522, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:400, and where b is greater than or equal to a + 14.	H72563, AA160114, AA159654, AA161261, AA165097, AA223618, AA243203
832554	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1356 of SEQ ID NO:401, b is an integer of 15 to 1370, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:401, and where b is greater than or equal to a + 14.	
832569	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1398 of SEQ ID NO:402, b is an integer of 15 to 1412, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:402, and where b is greater than or equal to a + 14.	
832578	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1736 of SEQ ID NO:403, b is an integer of 15 to 1750, where both a and b correspond to the positions of nucleotide	R09545, R09658, R09967, R11471, R16714, R16910, R16965, R19372, R80788, R80988, H28725, H63085, H63169, H75499, H75500, N33554, N41536, N52961, N52966, N74070, W01039, W57770, W57843, W60109,



	residues shown in SEQ ID NO:403, and where b is greater than or equal to a + 14.	W91978, W92107, AA001984, AA004653, AA027155, AA418427, AA281395, AA532870, AA564737, AA588889, AA631841, AA639548, AA765363, AA877896, AA887900, AA974026, A1057270, A1084214, A1094490, A1096750, A1097632, A1096745
832615	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1325 of SEQ ID NO:404, b is an integer of 15 to 1339, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:404, and where b is greater than or equal to a + 14.	
832620	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 468 of SEQ ID NO:405, b is an integer of 15 to 482, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:405, and where b is greater than or equal to a + 14.	
832632	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1399 of SEQ ID NO:406, b is an integer of 15 to 1413, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:406, and where b is greater than or equal to a + 14.	
832633	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1679 of SEQ ID NO:407, b is an integer of 15 to 1693, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:407, and where b is greater than or equal to a + 14.	R69173, AA053085, AA053597, AA427705, AA730380, AA865757, AA911497, A1083906
833483	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1328 of SEQ ID NO:408, b is an integer of 15 to 1342, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:408, and where b is greater than or equal to a + 14.	
834574	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2403 of SEQ ID NO:409, b is an integer of 15 to 2417, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:409, and where b is greater than or equal to a + 14.	
834859	Preferably excluded from the present invention are	

	one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1387 of SEQ ID NO:410, b is an integer of 15 to 1401, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:410, and where b is greater than or equal to a + 14.	
834861	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 3002 of SEQ ID NO:411, b is an integer of 15 to 3016, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:411, and where b is greater than or equal to a + 14.	
834890	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 944 of SEQ ID NO:412, b is an integer of 15 to 958, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:412, and where b is greater than or equal to a + 14.	T40255, T40256, T40770, T40778, T40803, T41118, T94280, T94627, R13201, R32388, R32389, R53769, H28669, H39502, H42532, H42533, R82957, R85205, R85206, R88749, R90730, R90754, R91006, R92221, H56130, H56210, H58500, H57659, H69479, H69882, N22547, N31579, N42592, N45537, N48687, N56654, N58050, N69059, N73728, N80748, N92927, N94545, W20471, W30838, W52039, W60171, W68292, W93085, W93140, N91563, AA010850, AA011289, AA054592, AA054780, AA081135, AA081214, AA081655, AA081936, AA082127, AA082262, AA088665, AA088804, AA102560, AA100239, AA114237, AA115714, AA115715, AA127304, AA127303, AA147789, AA148021, AA149821, AA152050, AA160878, AA169126, AA171659, AA172131, AA172285, AA194597, AA243129, AA419357, AA425135, AA426203, AA244212, AA505963, AA508221, AA527434, AA527878, AA565036, F17736, AA582605, AA582728, AA583851, AA586421, AA601920, AA570580, AA574367, AA577515, AA577538, AA565998, AA657417, AA659655, AA662658, AA665113, AA714991, AA770684, AA808865, AA826971, AA838507, AA876809, AA877842, AA878025, AA886042, AA886643, AA877950, AA937751, AA948428, AA947036, AA973473, AA983150, AA989361, A1082367, D78922, D82096, N83321, C04115, R29685, C17110, C18023, C18068, AA093539, AA094947, AA151399, AA654145, AA654136
835079	Preferably excluded from the present invention are	N25566, W00985, AA081340,

	one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 486 of SEQ ID NO:413, b is an integer of 15 to 500, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:413, and where b is greater than or equal to a + 14.	AA152231, AA164282, AA171619, AA187113, A1073932
835554	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 3383 of SEQ ID NO:414, b is an integer of 15 to 3397, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:414, and where b is greater than or equal to a + 14.	
835560	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2866 of SEQ ID NO:415, b is an integer of 15 to 2880, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:415, and where b is greater than or equal to a + 14.	
835723	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1602 of SEQ ID NO:416, b is an integer of 15 to 1616, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:416, and where b is greater than or equal to a + 14.	T71562, R11480, R19383, R25309, R46659, R48802, R48913, R50038, R50376, R54963, R46659, R70030, R70077, R70161, R71380, R72303, R72352, R72772, R72773, R73386, R73387, H15775, H15776, H25239, H27204, H30499, H42026, H42613, H43207, H43254, H44314, H44936, H44975, R98394, R98395, R99071, R99271, H58902, H58903, H73590, H73436, H75566, H80599, N40440, N48475, N59703, AA515035, AA515043, AA515450, AA515650, AA515746, AA551788, AA551943, AA554602, AA557281, AA581549, AA581554, AA587399, AA593890, AA593997, AA593998, AA568878, AA568962, AA622458, AA714206, AA728962, AA737738, AA738036, AA738486, AA847538, AA865069, AA872029, AA886612, AA903381, AA916458, AA916464, AA922563, AA928617, AA928314, AA934581, AA973769, AA973767, AA983480, AA991199, AA994932, AA995182, AA999704, A1028371, AA643041
835791	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1801 of SEQ ID NO:417, b is an integer of 15 to 1815, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:417, and where b is greater than or equal to a + 14.	

835817	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1952 of SEQ ID NO:418, b is an integer of 15 to 1966, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:418, and where b is greater than or equal to a + 14.	
835840	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2838 of SEQ ID NO:419, b is an integer of 15 to 2852, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:419, and where b is greater than or equal to a + 14.	T66583, R15957, R22860, R62339, R62341, R62856, AA210836, AA214633, AA256340, AA732582, AA740735
836048	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2691 of SEQ ID NO:420, b is an integer of 15 to 2705, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:420, and where b is greater than or equal to a + 14.	
836898	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1887 of SEQ ID NO:421, b is an integer of 15 to 1901, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:421, and where b is greater than or equal to a + 14.	
836927	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2463 of SEQ ID NO:422, b is an integer of 15 to 2477, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:422, and where b is greater than or equal to a + 14.	
837344	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 763 of SEQ ID NO:423, b is an integer of 15 to 777, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:423, and where b is greater than or equal to a + 14.	
837789	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1635 of SEQ ID NO:424, b is an integer of 15 to 1649, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:424, and where b is greater than or equal to a + 14.	
838549	Preferably excluded from the present invention are	

	one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1594 of SEQ ID NO:425, b is an integer of 15 to 1608, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:425, and where b is greater than or equal to a + 14.	
838754	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1780 of SEQ ID NO:426, b is an integer of 15 to 1794, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:426, and where b is greater than or equal to a + 14.	
838768	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 756 of SEQ ID NO:427, b is an integer of 15 to 770, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:427, and where b is greater than or equal to a + 14.	
839486	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 498 of SEQ ID NO:428, b is an integer of 15 to 512, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:428, and where b is greater than or equal to a + 14.	
839561	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1456 of SEQ ID NO:429, b is an integer of 15 to 1470, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:429, and where b is greater than or equal to a + 14.	R61634, AA135004, AA159213
839816	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 420 of SEQ ID NO:430, b is an integer of 15 to 434, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:430, and where b is greater than or equal to a + 14.	
840068	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1809 of SEQ ID NO:431, b is an integer of 15 to 1823, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:431, and where b is greater than or equal to a + 14.	
840279	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide	

	sequence described by the general formula of a-b, where a is any integer between 1 to 3377 of SEQ ID NO:432, b is an integer of 15 to 3391, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:432, and where b is greater than or equal to a + 14.	
840489	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2539 of SEQ ID NO:433, b is an integer of 15 to 2553, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:433, and where b is greater than or equal to a + 14.	
840538	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2518 of SEQ ID NO:434, b is an integer of 15 to 2532, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:434, and where b is greater than or equal to a + 14.	<p>T47551, T47552, T64522, T65947, R70190, H97064, N25641, N34240, N48063, N53261, N67904, N92702, N98774, W16899, W20316, W31028, W40137, W45371, W48722, W48577, W68670, W68773, W74242, AA033573, AA033574, AA063270, AA063271, AA065213, AA064894, AA082200, AA083707, AA085441, AA085694, AA088302, AA088303, AA099844, AA099984, AA102604, AA111894, AA112981, AA115039, AA115800, AA115799, AA122221, AA126905, AA126955, AA127109, AA127548, AA127549, AA128933, AA129152, AA129743, AA133290, AA135251, AA151963, AA156321, AA156382, AA160182, AA165104, AA164688, AA173757, AA180038, AA182644, AA190866, AA190959, AA191561, AA191637, AA197348, AA195895, AA258593, AA258622, AA262173, AA464978, AA465047, AA417938, AA418116, AA292727, AA523585, AA525020, AA548516, AA551816, AA554642, AA581720, AA568802, AA579801, AA738216, AA832441, AA903391, AA938688, AA977201, AA987552, A1095102, A1084149, W27768, C05889, C06263, AA089556, AA652586, AA213999, AA213977, AA219123, AA219290, AA435695, D12383, D12389, AA451677, AA453222, AA485641, AA485768, AA488670, AA485947, AA486053, AA486197, AA489511, AA489512, AA489558, AA491452, AA489876, AA600130, AA608644, AA620481, AA664307, AA629754, AA629909, AA677148, AA722910, AA772440, AA773550, A1038219, A1075755, A1081932, A1084706, T10852, T24678, F00208, F00897</p>

840545	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1808 of SEQ ID NO:435, b is an integer of 15 to 1822, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:435, and where b is greater than or equal to a + 14.	
840549	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1016 of SEQ ID NO:436, b is an integer of 15 to 1030, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:436, and where b is greater than or equal to a + 14.	R10733, T86298, R55182, R55183, H00476, H00530, H25856, H25909, H25910, N50923, W84600, W84452, AA227897, D78774, AA486440, AA629249
840551	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1618 of SEQ ID NO:437, b is an integer of 15 to 1632, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:437, and where b is greater than or equal to a + 14.	
840557	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1002 of SEQ ID NO:438, b is an integer of 15 to 1016, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:438, and where b is greater than or equal to a + 14.	
840561	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 580 of SEQ ID NO:439, b is an integer of 15 to 594, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:439, and where b is greater than or equal to a + 14.	
840562	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1566 of SEQ ID NO:440, b is an integer of 15 to 1580, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:440, and where b is greater than or equal to a + 14.	R08937, R09046, R14796, R18307, R31150, R42283, R51828, R54224, R42283, R72104, R72156, R73118, R73171, R73943, H25904, H27191, H27192, H30471, H72478, H72879, H88214, H98231, W45061, W45071, W49842, W67423, W67424, W93880, W94151, AA023007, AA022473, AA032224, AA032282, AA034411, AA035691, AA040428, AA046861, AA046994, AA046313, AA046139, AA053780, AA101657, AA101658, AA167298, AA227543, AA227684, AA458877, AA459067, AA463656, AA464047, AA464754, AA225370, AA225425, AA225400, AA558796, AA582089, AA565830, AA713907.

		AA864510, AA936117, C01002, N86320, C04277, AA652714, AA402391, AA402565, AA479073, AA621791, AA670200, AA456544, AA676732, AA707089, A1014599, A1022852, A1023739, A1091873, A1094288, Z39517, Z43438
840564	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1068 of SEQ ID NO:441, b is an integer of 15 to 1082, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:441, and where b is greater than or equal to a + 14.	
840572	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1227 of SEQ ID NO:442, b is an integer of 15 to 1241, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:442, and where b is greater than or equal to a + 14.	T87514, T87515, H84879, AA001503, AA506411, AA508167, AA715396, AA931268, AA292666, AA478036, AA478193, AA478194, AA707886, AA724969, AA725050, AA779127, AA843885
840600	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 954 of SEQ ID NO:443, b is an integer of 15 to 968, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:443, and where b is greater than or equal to a + 14.	R38172, AA226748, AA484320, AA831852
840604	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1346 of SEQ ID NO:444, b is an integer of 15 to 1360, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:444, and where b is greater than or equal to a + 14.	
840608	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1821 of SEQ ID NO:445, b is an integer of 15 to 1835, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:445, and where b is greater than or equal to a + 14.	
840620	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1341 of SEQ ID NO:446, b is an integer of 15 to 1355, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:446, and where b is greater than or equal to a + 14.	R17303, R41982, R41982, H43756, N62762, AA053677, AA053697, AA084224, AA084019, AA084952, AA419123, AA419160, AA426014, AA425077, AA427847, AA524035, AA565019, AA632254, AA745726, AA835832, AA931712, AA932520, AA937139, AA961716, AA995607, AA453838, AA455030, AA476981, AA479615, AA482659, AA455837,



		AA488554, AA620470, AA781416, AA844227, A1090902, T19161
840625	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 361 of SEQ ID NO:447, b is an integer of 15 to 375, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:447, and where b is greater than or equal to a + 14.	
840626	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1379 of SEQ ID NO:448, b is an integer of 15 to 1393, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:448, and where b is greater than or equal to a + 14.	
840638	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1649 of SEQ ID NO:449, b is an integer of 15 to 1663, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:449, and where b is greater than or equal to a + 14.	H01158, H01159, H05751, H05858, H83341, H83695, N47512, N47513, W39756, W79733, W90027, W90155, AA047691, AA047741, AA086374, AA100549, AA159315, AA159414, AA282525, AA282633, AA595381, AA688093, AA744757, AA865203, AA933811, AA969838, AA975917, F18424, D12197, D12219, AA478596, AA665540, AA909221, AA969720, A1049820
840649	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1366 of SEQ ID NO:450, b is an integer of 15 to 1380, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:450, and where b is greater than or equal to a + 14.	R00133, R22651, R44356, R44356, R56353, R93194, N47106, N50316, N50780, N55139, AA010596, AA010597, AA012940, AA012888, AA013216, AA013313, AA017544, AA017417, AA047814, AA047792, AA235545, AA262268, AA262879, AA563873, AA570239, AA573586, AA827412, AA862337, AA902472, AA962409, AA971292, AA973596, A1056509, A1080455, AA410833, T23822, T16761
840651	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 912 of SEQ ID NO:451, b is an integer of 15 to 926, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:451, and where b is greater than or equal to a + 14.	
840666	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1628 of SEQ ID NO:452, b is an integer of 15 to 1642, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:452, and where b is greater than or equal to a + 14.	N32778, N34353, N34537, N41780, N42818, N93337, W25190, AA035229, AA035230, AA044070, AA044162, AA195074, AA195174, AA419441, AA731906, AA761315, AA761330, AA766382, AA766593, AA769537, AA805515, AA806516, AA809893, AA814954, AA857917, N44554,

		AA393941, A1074651, T10618, Z35722
840681	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2240 of SEQ ID NO:453, b is an integer of 15 to 2254, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:453, and where b is greater than or equal to a + 14.	
840682	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1917 of SEQ ID NO:454, b is an integer of 15 to 1931, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:454, and where b is greater than or equal to a + 14.	
840684	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 757 of SEQ ID NO:455, b is an integer of 15 to 771, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:455, and where b is greater than or equal to a + 14.	
840697	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1155 of SEQ ID NO:456, b is an integer of 15 to 1169, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:456, and where b is greater than or equal to a + 14.	R00751, R02584, R02703, R69879, R69927, H13156, H29249, H29248, H41216, R83398, H54666, H54667, H73551, H73552, H90468, H91760, H97869, N31729, N31735, N51232, W32147, W32175, W44313, W45660, W57760, W57761, W68386, W68502, W68752, W68835, W72538, W76163, AA035740, AA043246, AA043585, AA044419, AA043053, AA047593, AA047601, AA088798, AA147253, AA155747, AA160105, AA165689, AA172386, AA173747, AA189005, AA189006, AA471066, AA507210, AA513086, AA516406, AA514685, AA635861, AA657400, AA668796, AA737126, AA768005, AA768358, AA887459, AA977176, D80509, D81008, D81471, D81800, D82666, N83795, AA643662, AA284937, AA290823, AA447984, AA448126, AA676807, AA709464, AA780333, AA843801, AA853391, AA868403, AA917460, T17166, T17177, T16671, T48481, T48507
840698	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 3235 of SEQ ID NO:457, b is an integer of 15 to 3249, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:457, and where b is	

	greater than or equal to $a + 14$ .	
840708	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1902 of SEQ ID NO:458, b is an integer of 15 to 1916, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:458, and where b is greater than or equal to $a + 14$ .	R21272, R45362, R45362, H06049, H13385, AA082768, AA101114, AA131634, AA131718, AA152290, AA150232, AA418083, AA418230, AA422115, AA424919, AA426139, AA741277, AA749290, AA811505, AA836102, AA411231, AA453804, AA453890, AA758905, AA769817, AA770192, AA904708, AA905158, AA969156, A1093952, Z42470, Z41665, Z44053
840714	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2759 of SEQ ID NO:459, b is an integer of 15 to 2773, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:459, and where b is greater than or equal to $a + 14$ .	
840716	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2017 of SEQ ID NO:460, b is an integer of 15 to 2031, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:460, and where b is greater than or equal to $a + 14$ .	
840721	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1825 of SEQ ID NO:461, b is an integer of 15 to 1839, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:461, and where b is greater than or equal to $a + 14$ .	
840735	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 765 of SEQ ID NO:462, b is an integer of 15 to 779, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:462, and where b is greater than or equal to $a + 14$ .	T47277, T56085, T93319, T85388, H57620, H58465, N77902, N80219, N93978, W19715, W37380, W37643, W38508, W38722, W47048, W68079, W67976, W69349, W69350, AA025313, AA024560, AA063371, AA063370, AA463222, AA463223, AA424422, AA469264, AA480510, AA507733, AA524348, AA557233, AA602394, AA603318, AA631014, AA569554, AA575944, AA688112, AA911131, AA932225, AA937015, AA994856, A1077707, N92552, W00604, C00184, AA292823, AA401683, AA663906, AA664122, AA771943, AA779608, AA812529, A1028120, A1027559, A1032511, A1033880, A1034204, A1078458, A1041685, D31473, T64469
840738	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide	

	sequence described by the general formula of a-b, where a is any integer between 1 to 1703 of SEQ ID NO:463, b is an integer of 15 to 1717, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:463, and where b is greater than or equal to a + 14.	
840745	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 814 of SEQ ID NO:464, b is an integer of 15 to 828, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:464, and where b is greater than or equal to a + 14.	
840747	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1159 of SEQ ID NO:465, b is an integer of 15 to 1173, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:465, and where b is greater than or equal to a + 14.	
840756	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 507 of SEQ ID NO:466, b is an integer of 15 to 521, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:466, and where b is greater than or equal to a + 14.	AA074254
840776	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1414 of SEQ ID NO:467, b is an integer of 15 to 1428, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:467, and where b is greater than or equal to a + 14.	T47069, T47068, T63511, T63587, T79637, T79722, R36141, R36419, R65831, R65934, R69612, R69701, H00464, H00514, H04572, H04575, H12602, H12652, H13166, H66218, H67195, H67868, H67868, N62959, W92249, W92250, W92609, W95234, AA007598, AA193373, AA195360, AA195359, AA425046, AA430627, AA428172, AA484871, AA557201, AA902998, AA927360, N79862, AA479674, AA477192, AA481418, AA481651, AA495983, AA496377, AA496655, AA912146, AA912181, AI049805, AA693485
840784	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 3449 of SEQ ID NO:468, b is an integer of 15 to 3463, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:468, and where b is greater than or equal to a + 14.	
840788	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 607 of SEQ ID	

	NO:469, b is an integer of 15 to 621, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:469, and where b is greater than or equal to $a + 14$ .	
840794	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1819 of SEQ ID NO:470, b is an integer of 15 to 1833, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:470, and where b is greater than or equal to $a + 14$ .	
840797	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 3188 of SEQ ID NO:471, b is an integer of 15 to 3202, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:471, and where b is greater than or equal to $a + 14$ .	
840799	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 927 of SEQ ID NO:472, b is an integer of 15 to 941, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:472, and where b is greater than or equal to $a + 14$ .	
840818	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1265 of SEQ ID NO:473, b is an integer of 15 to 1279, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:473, and where b is greater than or equal to $a + 14$ .	
840822	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 3195 of SEQ ID NO:474, b is an integer of 15 to 3209, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:474, and where b is greater than or equal to $a + 14$ .	T47621, T77305, T83423, R18484, R51973, R51974, R73192, H06082, H12940, H27135, H45895, H45904, N72089, W00342, W52213, W96404, AA045488, AA058907, AA062768, AA069032, AA081439, AA082427, AA084417, AA101216, AA234022, AA534011, AA565390, AA588319, AA588430, AA568701, AA635907, AA579930, AA827039, AA857519, AA872490, AA904077, AA995057, A1073336, N95359, C15883, AA781445, AA906492, A1037943, A1039428
840830	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 819 of SEQ ID NO:475, b is an integer of 15 to 833, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:475, and where b is	N33920, N33932, N49642, N49629, AA508747, AA514767, AA583465, AA805203, AA878968, U37231, T24573

	greater than or equal to $a + 14$ .	
840846	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1127 of SEQ ID NO:476, b is an integer of 15 to 1141, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:476, and where b is greater than or equal to $a + 14$ .	T68706, T68719, T68771, T68784, T73424, T73431, T73486, T73492, T73499, T73535, T89865, R11465, T79345, T79774, T81799, T82119, T82855, T96198, T96454, T96686, T96802, T96920, T97027, T99996, T99997, R00156, R00157, R83404, R85816, R91357, R93314, R94713, R94794, R97348, R99024, R99798, H48280, H48369, H48754, H54738, H54739, H55985, H55984, H56050, H56244, H57662, H57872, H57873, H58502, H60170, H60211, H62933, H69203, H69228, H69229, H71630, H73011, H73012, H81193, H81194, H90826, H91385, N33963, N49672, N49822, N52577, N54836, N58435, N64440, N66934, N69249, N69373, N74062, N75759, N78025, N78145, N94249, N95116, W03303, W01169, W01912, N91401, AA025243, AA026028, AA193126, AA194255, AA236507, AA242995, AA622239, AA575858, AA575872, AA576026, AA576150, AA576597, AA864932, AA877934, AA969761, AA994970, AI017867, D82634, C21067, AA431221, AA779655, AA782374, AA812640, AA923315, AA962377, AA993251, AI018445, AI025584, AI092470, T79311
840848	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1088 of SEQ ID NO:477, b is an integer of 15 to 1102, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:477, and where b is greater than or equal to $a + 14$ .	R10066, R10163, T26606, R61067, R72646, H08322, H47858, H47859, R86048, H68866, H68867, H69098, H82364, N58491, N78080, W52876, W60083, AA043086, AA045865, AA045866, AA055712, AA057298, AA058743, AA079887, AA079888, AA099233, AA099234, AA102153, AA113213, AA115932, AA121000, AA131067, AA143412, AA146598, AA155632, AA155688, AA160447, AA173257, AA173248, AA195987, AA196375, AA233537, AA463552, AA503072, AA551794, AA586410, AA594814, AA613123, AA573356, AA580449, AA731195, AA742856, AA827930, AA863440, AA865529, AA876847, AA953614, AA976924, N84278, N88762, C17112, AA219765, AA284503, AA293437, AA293046, AA669435, AA722103, AI027785, AI073617, AI092707, T17392, F08770, D12026
840860	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide	T89645, T89919, T93704, R21871, R22387, R78094, R78181, R78515,

	<p>sequence described by the general formula of a-b, where a is any integer between 1 to 4187 of SEQ ID NO:478, b is an integer of 15 to 4201, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:478, and where b is greater than or equal to a + 14.</p>	<p>R78560, H40124, H41731, N28359, N42893, N62851, N64787, N67463, N76199, N77065, N77758, W67341, W68381, AA034244, AA044935, AA045056, AA057392, AA057684, AA071214, AA071442, AA081937, AA082360, AA082229, AA082230, AA082708, AA083297, AA083188, AA127585, AA149575, AA151791, AA167113, AA173360, AA191227, AA195437, AA223329, AA223614, AA243268, AA261939, AA262815, AA262816, AA422160, AA426276, AA225924, AA504466, AA504634, AA522823, AA554566, AA632813, AA576873, AA662886, AA730326, AA748669, AA828942, AA837197, AA857065, AA857683, AA862276, AA864246, AA873317, A1083733, D82604, D82635, N81179, N85023, N85166, N85712, C00193, C00199, C02425, N87331, N88683, N88852, N89408, C02916, C05151, C06382, AA642209, C21319, AA091285, AA091688, AA094300, AA205974, AA206268, AA206598, AA205324, AA649340, AA247212, AA404505, AA421263, AA421361, D11545, AA441853, AA441826, AA463350, AA463858, AA487271, AA487388, AA496439, AA496488, AA634627, AA663685, AA665466, AA456144, AA722996, AA772136, AA772153, AA774179, AA992418, A1076734, T10506, Z30218, Z38961, T16262, T48571, D31110, D45597, F06042, F00682</p>
840861	<p>Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 773 of SEQ ID NO:479, b is an integer of 15 to 787, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:479, and where b is greater than or equal to a + 14.</p>	<p>T52180, T52256, T57048, T60934, T60993, T94137, T94228, T91060, T85924, R23216, R23292, R31316, R31576, R62640, R62693, H03198, H18231, H18269, H22414, H26112, H26116, H26378, H40754, H38895, H47721, H48072, R89134, R89141, R91829, R91836, R98452, H65626, H65627, H69728, H71913, H71914, H78844, H80090, H83062, H84585, H87467, H87577, H93457, H93458, N23179, N30549, N32644, N39052, N40455, N48060, N48244, N53258, N53755, N63557, N94559, N94883, N94981, N95791, N42987, W19445, W19573, W23831, W24902, W30850, W32700, W32701, W37523, W56867, W60497, W60972, W61219, W69268, W69346, W80426, W80556, W94817, W95832, W95966, W96035, W96092,</p>

		N90310, AA010147, AA010148, AA025440, AA025757, AA027347, AA027822, AA027874, AA029650, AA029651, AA037779, AA039260, AA046801, AA046818, AA054707, AA058654, AA062684, AA063287, AA074876, AA074979, AA084381, AA085264, AA085328, AA085598, AA122190, AA120978, AA133892, AA129630, AA172403, AA172206, AA190489, AA190525, AA464455, AA464996, AA225769, AA259210, AA483109, AA483741, AA493542, AA502162, AA516183, AA522567, AA526813, AA557654, AA588882, AA593799, AA576216, AA659530, AA662308, AA688246, AA688254, AA687457, AA687516, AA689236, AA728852, AA729032, AA747479, AA747979, AA831447, AA887348, AA903105, AA916516, AA934714, AA953363, AA976759, AA991410, AA991434, AI002147, AI028033, N83338, C02469, R29174, AA090669, AA092066, AA648634, AA443968, AA444149, AA482243, AA482340, AA485406, AA598458, AA644566, AA664032, AA680199, AA676482, AA629708, AA630110, AA457100, AA431269, AA405296, AA405332, AA721997, AA724146, AA774657, AA781529, AA781641, AA781838, AA782849, AA813171, AA843229, AA846744, AA846814, AA854299, AA854765, AA789029, AA993047, AI023973, AI027725, AI031943, AI038463, AI041602, AI085085, AI086504, AI088189
840871	<p>Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 717 of SEQ ID NO:480, b is an integer of 15 to 731, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:480, and where b is greater than or equal to a + 14.</p>	H42821, AA028094, AA099211, AA160368, AA223572, AA232552, AA252811
840874	<p>Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1105 of SEQ ID NO:481, b is an integer of 15 to 1119, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:481, and where b is greater than or equal to a + 14.</p>	
840878	<p>Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b,</p>	T40405, T41252, T47240, T47241, T50233, T52891, T57110, T58359, R19508, R43858, R43858, R75598,



	where a is any integer between 1 to 2042 of SEQ ID NO:482, b is an integer of 15 to 2056, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:482, and where b is greater than or equal to a + 14.	R75665, H13192, H13193, N25264, N31900, N42683, N72995, N93388, W25360, W47628, W47629, AA009691, AA009410, AA045777, AA045910, AA063040, AA063076, AA130044, AA149205, AA149206, AA191678, AA252698, AA464304, AA225264, AA514845, AA526726, AA548411, AA548704, AA552050, AA552558, AA568675, AA827017, AA834447, AA838450, AA886357, AA886653, AA887879, AA916602, AA928685, AA968793, A1005016, W28859, AA134038, AA455118, AA496380, AA496656, AA598830, AA653270, AA725217, AA733068, A1004394, A1023815, A1026954, A1040891, Z25388, Z28470, AA702322
840880	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 873 of SEQ ID NO:483, b is an integer of 15 to 887, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:483, and where b is greater than or equal to a + 14.	H02306, H02418, N48196, N53344, AA059013, AA506159, AA613938, AA662759, AA976725, AA854631
840884	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1864 of SEQ ID NO:484, b is an integer of 15 to 1878, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:484, and where b is greater than or equal to a + 14.	
840907	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1552 of SEQ ID NO:485, b is an integer of 15 to 1566, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:485, and where b is greater than or equal to a + 14.	
840926	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 3032 of SEQ ID NO:486, b is an integer of 15 to 3046, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:486, and where b is greater than or equal to a + 14.	
840932	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1890 of SEQ ID NO:487, b is an integer of 15 to 1904, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:487, and where b is	

	greater than or equal to $a + 14$ .	
840940	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 813 of SEQ ID NO:488, b is an integer of 15 to 827, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:488, and where b is greater than or equal to $a + 14$ .	
840947	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1912 of SEQ ID NO:489, b is an integer of 15 to 1926, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:489, and where b is greater than or equal to $a + 14$ .	
840959	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1447 of SEQ ID NO:490, b is an integer of 15 to 1461, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:490, and where b is greater than or equal to $a + 14$ .	
840964	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 791 of SEQ ID NO:491, b is an integer of 15 to 805, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:491, and where b is greater than or equal to $a + 14$ .	R79226, H12332, H51062, H83364, H89523, N27508, N30527, N40233, N52503, N53855, N94367, AA055215, AA055306, AA188169, AA468498, AA470473, AA563662, AA622643, AA579613, AA668790, AA748160, AA765447, AA873430, AA879079, AA903275, AA970424, N73354, AA402259, AA883758, AA890505, AA906005, AI023931
840979	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2255 of SEQ ID NO:492, b is an integer of 15 to 2269, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:492, and where b is greater than or equal to $a + 14$ .	
840984	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 4094 of SEQ ID NO:493, b is an integer of 15 to 4108, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:493, and where b is greater than or equal to $a + 14$ .	
840986	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2195 of SEQ ID NO:494, b is an integer of 15 to 2209, where both a and b correspond to the positions of nucleotide	H25393, H25394, H25511, H25512, R95750, R95794, H64076, H64131, H68715, H80548, H80604, H94681, H95039, H99481, N28293, N30167, N35782, W47389, W47262, W61304, W65368, AA054346, AA054383.

	residues shown in SEQ ID NO:494, and where b is greater than or equal to a + 14.	AA058320, AA058448, AA512954, AA558416, AA588459, AA935690, AI097565, N87339, AA993027, AA993568, AA701454, AA702350
840988	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1663 of SEQ ID NO:495, b is an integer of 15 to 1677, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:495, and where b is greater than or equal to a + 14.	T87048, R24473, R43337, R43337, N75007, W05750, AA182467, AA227466, AA504464, AA504538, AA923479, AA648887, AA663889, AI027636, AI028506, AI026720, Z42717
840990	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1688 of SEQ ID NO:496, b is an integer of 15 to 1702, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:496, and where b is greater than or equal to a + 14.	
840992	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2362 of SEQ ID NO:497, b is an integer of 15 to 2376, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:497, and where b is greater than or equal to a + 14.	
841009	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 826 of SEQ ID NO:498, b is an integer of 15 to 840, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:498, and where b is greater than or equal to a + 14.	T40334, T41195, T79150, T79231, T85615, T98895, T99485, R25796, H03311, H03312, H11314, H21245, R91754, R91755, R93025, R97834, R97886, R99577, R99583, R99683, R99689, H88057, H97799, H97870, N34019, N35363, N42786, N44738, N52502, N70158, N72884, N74746, N93542, N95357, N98354, W01181, W03108, W15165, W19587, W21350, W24700, W24805, W39226, W48682, W49637, W49739, W51977, W67546, W67528, W67665, W79731, W93828, W93829, AA025348, AA025356, AA024401, AA024402, AA029589, AA029588, AA099331, AA099865, AA121627, AA126717, AA126816, AA126817, AA133155, AA165162, AA165163, AA557332, AA640015, AA579505, AA665011, AA665221, AA738009, AA830748, AA918150, AA918992, AA947223, AA974955, AI083731, N56157, N89240, AA092060, AA094384, AA650291, AA292814, AA402491, F20671, F21115, D11655, D11564, D11605, D12048, AA634049, U54738, AA732766, AA782030, AA843638, AA860477, AA861482, AI018649,

		A1092171, Z28714, T23956, AA694568
841012	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 447 of SEQ ID NO:499, b is an integer of 15 to 461, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:499, and where b is greater than or equal to a + 14.	
841016	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2768 of SEQ ID NO:500, b is an integer of 15 to 2782, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:500, and where b is greater than or equal to a + 14.	R21854, R21868, R23349, R27518, R63726, R63775, R65731, R65957, R65958, R66192, R66977, R66978, R67072, R69600, R69690, H12415, H12416, N46541, N47260, N47778, N48572, N51984, N95008, W25613, W31713, W32142, W38029, W38650, W38655, AA034256, AA037658, AA037660, AA039268, AA042908, AA042921, AA063533, AA126558, AA130121, AA130157, AA137270, AA136020, AA232954, AA233044, AA429346, AA429872, AA565520, AA604780, AA610435, AA631349, AA631518, AA740206, AA770618, AA912228, A1079705, N84191, N85956, N92894, W38030, C00380, N83173, C03262, AA092010, U82782, AA247592, AA284977, AA283619, AA291890, AA293636, AA410312, AA410537, AA453566, AA487623, AA626442, AA628932, AA629190, AA629753, AA629916, AA719528, AA843073, AA844228, AA890492, A1024670, A1051881, A1061324, T11149
841017	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1235 of SEQ ID NO:501, b is an integer of 15 to 1249, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:501, and where b is greater than or equal to a + 14.	R21764, R21815, N71125, W17312, AA112660, AA179538, AA179507, AA902202, AA907419, AA913594, AA994481, A1049652
841021	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1344 of SEQ ID NO:502, b is an integer of 15 to 1358, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:502, and where b is greater than or equal to a + 14.	R23836, W38704, AA033686, AA176734, AA192268, AA525913, AA531505, AA532666, AA533781, AA533827, AA533949, AA554396, AA576754, AA906883, N24273, C14272, C14285, C14286, C18998
841032	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 487 of SEQ ID NO:503, b is an integer of 15 to 501, where both a and b correspond to the positions of nucleotide	T41136, T52990, T52991, T61494, T63001, T63145, T87321, T87328, T89480, T84361, R05264, N75935, W05120, W25352, AA191627, AA258512, AA418549, AA224774, AA225253, AA229538, AA229537,

	residues shown in SEQ ID NO:503, and where b is greater than or equal to a + 14.	AA229951, AA230318, AA468106, AA468170, AA482814, AA482855, AA482894, AA482906, AA483676, AA491563, AA491627, AA492175, AA501375, AA502205, AA505498, AA508058, AA508125, AA512979, AA513165, AA523347, AA528170, AA531497, AA542840, AA551430, AA553992, AA554420, AA582164, AA583205, AA593192, AA593362, AA602125, AA603378, AA603728, AA617691, AA622865, AA630937, AA631991, AA570802, AA569520, AA654990, AA664728, AA664864, AA665278, AA729616, AA729639, AA729652, AA730512, AA730705, AA730910, AA737300, AA737303, AA736808, AA736909, AA738098, AA740165, AA740553, AA742574, AA742885, AA746988, AA747057, AA747094, AA747099, AA747961, AA748108, AA804727, AA805835, AA834105, AA838466, AA864527, AA872303, AA875939, AA876612, AA876936, AA879219, AA885735, AA886033, AA888159, AA888528, AA888683, AA903652, AA935001, AA948734, AA947836, AA978250, AA994661, AI073926, AI085517, N83676, N86451, N87989, AA642538, AA090432, AA090481, AA092225, AA091643, AA094678, AA094818, AA095214, AA648652, AA649783, AA650377, AA401641, F21163, AA411822, AA442212, AA609798, AA679909, F22052, AA679265, AA722456, AI003421, AI028430, AI077884, AI086743, T89286, R05321, AA694044
841051	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1997 of SEQ ID NO:504, b is an integer of 15 to 2011, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:504, and where b is greater than or equal to a + 14.	AA427363
841064	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1975 of SEQ ID NO:505, b is an integer of 15 to 1989, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:505, and where b is greater than or equal to a + 14.	R95695, H49073, H61707, H61911, H68517, H89719, H89781, H89828, H90680, N76870, W88654, W88898, AA046748, AA053076, AA053592, AA127256, AA127257, AA187351, AA188218, H67307, AA602545, AA720701, AA742288, N87596, AA094084, AA204976, AA676787, AA703221, AA779414, AI038609, AI074626, AI088527, T17364,

		AA702787
841069	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1071 of SEQ ID NO:506, b is an integer of 15 to 1085, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:506, and where b is greater than or equal to a + 14.	
841072	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1471 of SEQ ID NO:507, b is an integer of 15 to 1485, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:507, and where b is greater than or equal to a + 14.	
841078	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1916 of SEQ ID NO:508, b is an integer of 15 to 1930, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:508, and where b is greater than or equal to a + 14.	T39937, T68962, T84426, R20697, R36425, R45643, R45643, R68137, R70943, R70957, R70996, R71011, H02222, H05658, H05659, H25177, H29362, H54732, H54733, H60311, H60310, H77561, H77562, H78245, H78446, H82436, H82699, N20477, N57742, N59418, N59709, N76617, AA029237, AA055009, AA055434, AA236337, AA425703, AA427773, AA482193, AA482287, AA612777, AA729757, AA737276, AA744359, AA872776, AA972581, C06045, AA446583, AA449748, AA707197, AA757691, AA774691, AA992571, A1003756, A1027513, A1039704, A1042272, A1052652, A1077380, A1083949, AA774036
841080	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1120 of SEQ ID NO:509, b is an integer of 15 to 1134, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:509, and where b is greater than or equal to a + 14.	
841088	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1368 of SEQ ID NO:510, b is an integer of 15 to 1382, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:510, and where b is greater than or equal to a + 14.	R00895, R21561, R42090, R42090, H05080, N79589, N94381, W16578, W42724, W42813, W46346, W46347, W47346, W57707, W57783, AA070469, AA490938, AA586820, AA580196, AA745683, AA809239, AA931405, D11601, AA725448, AA992145, A1023735, A1025359, A1031575, A1033697, A1038145, A1093535, F00072
841092	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1727 of SEQ ID	

	NO:511, b is an integer of 15 to 1741, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:511, and where b is greater than or equal to a + 14.	
841095	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1516 of SEQ ID NO:512, b is an integer of 15 to 1530, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:512, and where b is greater than or equal to a + 14.	W20114, AA255840, AA568302, AA406006, AA434170
841096	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2985 of SEQ ID NO:513, b is an integer of 15 to 2999, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:513, and where b is greater than or equal to a + 14.	
841102	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2034 of SEQ ID NO:514, b is an integer of 15 to 2048, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:514, and where b is greater than or equal to a + 14.	
841104	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 3286 of SEQ ID NO:515, b is an integer of 15 to 3300, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:515, and where b is greater than or equal to a + 14.	T93851, R05295, R05354, R71097, R71445, R99396, N53129, W38359, W38417, W38418, W39384, W44785, W44786, W69719, W69847, W73703, AA134718, AA164646, AA164647, AA418958, AA420439, AA420440, AA548241, AA548224, AA558195, W73847, Z19840, AA707354, AA868898, AA917430, A1073454, F09131, F11469, AA700476
841108	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 3411 of SEQ ID NO:516, b is an integer of 15 to 3425, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:516, and where b is greater than or equal to a + 14.	T89709, T89806, T91163, T93774, T93819, T95226, R06420, R06475, R23277, R23370, R32742, R32743, R52354, R52355, R64095, R64184, R65984, R65985, R70225, R70226, R76344, R76672, R80205, H00679, H00770, H04254, H24758, H24803, H40273, H38053, H38054, H47116, H47210, R92478, R94873, R94872, H57866, H57867, H59353, H61105, H63261, H63535, H63938, H67759, H67760, H77384, H77385, H82932, H87435, H87541, H88753, H88754, N59081, N59489, N63682, N63939, N66851, N70709, N92122, N99845, W32595, W88585, W90769, W90327, W93082, W93137, AA025425, AA041232, AA114914, AA114913, AA128525, AA235362, AA235944,

		AA235945, AA425197, AA636023, AA639557, AA729723, AA907495, AI056355, AI089809, AA448599, AA449742, AA476262, AA478567, AA478700, AA599706, AA634117, AA677126, AA716562, AA923333, AA948589, AI051569, AI073816, AI074666, AI080341, AI084428, AI090962, AI096407
841118	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1344 of SEQ ID NO:517, b is an integer of 15 to 1358, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:517, and where b is greater than or equal to a + 14.	R20815, R36529, R38448, R46586, R46586, R71122, R71625, R77658, R80438, R80643, H12595, H12644, H99733, N20132, N25939, N29738, N57157, N59874, N67154, N67834, W03438, W04625, W31524, AA044199, AA044996, AA135739, AA135782, AA146912, AA146911, AA173589, AA224431, AA232224, AA256600, AA256599, AA419270, AA419321, AA425195, AA484744, AA507823, AA513832, AA584296, AA600955, AA614813, AA807248, AA904059, AA937796, AA973678, AA983325, AA991604, W01284, C16969, AA476260, AA476318, AA476367, AA609550, AA678511, AA722726, AA904676, AA954468, AI001869, AI031538, Z41297
841119	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1354 of SEQ ID NO:518, b is an integer of 15 to 1368, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:518, and where b is greater than or equal to a + 14.	R18472, W39766, AA076303, AA985235
841124	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 919 of SEQ ID NO:519, b is an integer of 15 to 933, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:519, and where b is greater than or equal to a + 14.	
841137	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1416 of SEQ ID NO:520, b is an integer of 15 to 1430, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:520, and where b is greater than or equal to a + 14.	T65560, R52978, R59392, H24368, H25185, N33308, AA016160, AA019434, AA082036, AA099724, AA099725, AA101466, AA100553, AA100634, AA100635, AA143046, AA150250, AA151129, AA165491, AA172129, AA176104, AA176248, AA176272, AA197310, AA227454, AA232220, AA243156, AA261904, AA262541, AA458854, AA459044, AA481155, AA493247, AA514323, AA522820, AA558368, AA582973, AA604489, AA640528, AA569125,



		AA569824, AA737640, AA743846, AA808232, AA812222, AA847813, AA865060, AA872242, AA872353, AA922866, AA933823, AA988358, AI056397, AI085865, AI088865, AA205921, AA205923, AA205997, AA204887, AA205731, DI1887, AA634040, AA703823, AA703893, Z20424, AA707344, AA707416, AA716243, AA683201, AA890456, AI003274, AI076618, AI090177, TI0877, Z28746, T25145, Z40353, FI1026, F09670, AA699695, AA701137
841143	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1155 of SEQ ID NO:521, b is an integer of 15 to 1169, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:521, and where b is greater than or equal to a + 14.	T52948, T57468, T59332, T91403, T84637, R69314, R69315, R77481, R77675, R77676, H30692, H70576, N24036, N24905, N26173, N35858, N36029, W39771, W45303, W80648, W80649, AA029895, AA029983, AA036639, AA036850, AA043430, AA043431, AA046109, AA046196, AA076106, AA076107, AA083131, AA083181, AA083285, AA083293, AA147761, AA147804, AA155831, AA155741, AA430082, AA581553, AA593886, AA594233, AA604399, AA576339, AA715836, AA730946, AA737298, AA768251, AA872423, AA888276, AA961744, AA962699, AA975874, AI000132, R29417, AA640954, AA094702, AA398483, AA402600, AA489817, AA489948, AA496290, AA663953, AA663986, AA725581, AA771972, AA781165, AA845829, AA772618, AA773208, AA907551, AI003883, AI004593, AI031669, AI052123, AI085380
841148	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2148 of SEQ ID NO:522, b is an integer of 15 to 2162, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:522, and where b is greater than or equal to a + 14.	
841149	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 785 of SEQ ID NO:523, b is an integer of 15 to 799, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:523, and where b is greater than or equal to a + 14.	AA812937
841151	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b,	

	where a is any integer between 1 to 1708 of SEQ ID NO:524, b is an integer of 15 to 1722, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:524, and where b is greater than or equal to a + 14.	
841155	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 548 of SEQ ID NO:525, b is an integer of 15 to 562, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:525, and where b is greater than or equal to a + 14.	
841161	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2009 of SEQ ID NO:526, b is an integer of 15 to 2023, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:526, and where b is greater than or equal to a + 14.	H81836, AA015599, AA099033, AA099034, AA211818, AA741499, AA748367, AA768854, AA805297, AA804217, A1000120, A1090415, D79280, D79875, AA628397, AA628438, AA889584, Z36757
841162	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2833 of SEQ ID NO:527, b is an integer of 15 to 2847, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:527, and where b is greater than or equal to a + 14.	T54529, T54568, T39916, T40885, T64421, T64740, T94433, T94519, T94763, T94764, T67443, T67536, T69533, R08782, R08783, T84049, T86084, R18023, R19657, R33054, R33948, R52119, R52216, R53248, R53249, R71311, H04393, H04418, H23196, H23309, H47118, R95161, H54791, H54843, H66487, H66488, H87522, H87523, H92220, H97204, H97637, H98041, N25008, N27036, N32850, N32940, N41677, N41803, N52911, N55243, N55603, N59425, N62367, N67146, N67527, N68040, N68109, N69439, N79136, W03264, W02511, W16533, W16511, W16949, W19590, W20032, W25683, W56022, W57870, W58141, W84752, W84757, W96458, W96558, N89892, N91494, AA035714, AA040577, AA040675, AA043889, AA052991, AA053277, AA053702, AA062923, AA063530, AA074314, AA074909, AA074744, AA076274, AA098982, AA099025, AA146894, AA146893, AA160127, AA160126, AA160195, AA160196, AA169764, AA169385, AA179301, AA223348, AA233558, AA235471, AA460676, AA420533, AA506563, AA523418, AA527621, AA528362, AA531060, AA532619, AA541282, AA552184, AA564466, AA564790, H98795, AA583450, AA613483, AA622733, AA627809, AA577550, AA578980, AA579413, AA714153, AA721494, AA721786, AA737104,

		AA738062, AA745852, AA746662, AA748113, AA814512, AA814515, AA848156, AA858182, AA877787, AA886219, AA886814, AA908510, AA919073, AA953828, AA971838, AA974669, AA974937, AA975070, AA978156, AA985412, AA985429, AA989103, AA989168, AA975750, AI053418, AI053736, AI053892, AI053967, AI053988, AI054073, AI054111, F18748, AI096767, W16689, F17979, W26593, W74635, R29761, AA090571, AA090284, AA092279, AA092676, AA174176, AA206002, AA206857, AA206939, AA204847, AA204862, AA205665, AA205777, C17805, AA215924, AA284942, AA285094, AA292514, AA293872, AA398296, AA401676, AA412021, AA450108, AA450173, AA477960, AA478675, AA479216, AA482218, AA608548, AA634838, AA634910, AA634951, AA644321, AA664196, AA665979, AA668238, AA668579, AA669764, AA669856, AA676279, AA630300, Z20366, AA716371, AA716380, Z19906, AA777040, AA778451, AA781061, AA845834, T25435, Z21568, AA772588, AA917780, AI003327, AI016140, AI024969, AI032559, AI056850, AI088269, AI090536, AI092597, AI093387, T15364, D29035, T27400, T27473, F02321, F06069, T69476, AA773898, AA694154
841163	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 802 of SEQ ID NO:528, b is an integer of 15 to 816, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:528, and where b is greater than or equal to a + 14.	T70512, W58177, W58266, AA027003, AA047260, AA057146, AA076110, AA150122, AA150030, AA424246, AA425670, AA523788, AA554661, AA582491, AA587000, AA633476, AA578397, AA662364, AA687611, AA729856, AA741041, AA806947, AA894899, AA922687, AA934486, AA946779, AA954606, AA962108, AA988276, AI054171, AA436000, AA436099, AA442324, AA451996, AA722958, AA780203, T25797, AI018410, AI024726, AI074321
841169	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 871 of SEQ ID NO:529, b is an integer of 15 to 885, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:529, and where b is greater than or equal to a + 14.	
841172	Preferably excluded from the present invention are	T47968, H14181, H26893, N40884,

	one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 728 of SEQ ID NO:530, b is an integer of 15 to 742, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:530, and where b is greater than or equal to a + 14.	Z42735
841174	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 511 of SEQ ID NO:531, b is an integer of 15 to 525, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:531, and where b is greater than or equal to a + 14.	
841179	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1911 of SEQ ID NO:532, b is an integer of 15 to 1925, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:532, and where b is greater than or equal to a + 14.	
841183	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 488 of SEQ ID NO:533, b is an integer of 15 to 502, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:533, and where b is greater than or equal to a + 14.	
841186	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1786 of SEQ ID NO:534, b is an integer of 15 to 1800, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:534, and where b is greater than or equal to a + 14.	
841204	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2483 of SEQ ID NO:535, b is an integer of 15 to 2497, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:535, and where b is greater than or equal to a + 14.	
841206	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 4076 of SEQ ID NO:536, b is an integer of 15 to 4090, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:536, and where b is greater than or equal to a + 14.	
841207	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide	AA215286

	sequence described by the general formula of a-b, where a is any integer between 1 to 572 of SEQ ID NO:537, b is an integer of 15 to 586, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:537, and where b is greater than or equal to a + 14.	
841211	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1236 of SEQ ID NO:538, b is an integer of 15 to 1250, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:538, and where b is greater than or equal to a + 14.	
841225	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1336 of SEQ ID NO:539, b is an integer of 15 to 1350, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:539, and where b is greater than or equal to a + 14.	
841229	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2495 of SEQ ID NO:540, b is an integer of 15 to 2509, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:540, and where b is greater than or equal to a + 14.	
841237	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1729 of SEQ ID NO:541, b is an integer of 15 to 1743, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:541, and where b is greater than or equal to a + 14.	H39746, H38765, H53680, H84385, H84386, H95751, H96427, H96428, N22709, N24033, N27417, N27531, N31183, N34699, N35427, N40348, N46995, N47385, W47664, W52613, W58021, AA020909, AA032219, AA032277, AA036745, AA053732, AA055872, AA057318, AA062713, AA070398, AA134055, AA132315, AA132625, AA149601, AA149602, AA494458, AA516430, AA534386, AA582804, AA581987, AA588838, AA631158, AA635970, AA577392, AA577494, AA857008, AA894813, AA933084, A1000994, N47386, D11495, D11593, D12071, D11877, D11882, D11902, AA456436, AA683214, AA890528, AA983938, A1074406, A1084728
841241	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2196 of SEQ ID NO:542, b is an integer of 15 to 2210, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:542, and where b is greater than or equal to a + 14.	T64820, R18486, R48571, R48670, R51358, R51464, R70428, R71854, R77389, R77390, H18251, H18293, H18401, H18402, H19764, H19765, H21210, H21526, H24560, H25150, H26985, H28104, H30240, H30297, H30868, H30871, H40890, H41878, H41879, H43721, H43811, H43814,

		R84543, R85932, R87323, R93828, H49042, H49101, H51175, H51188, H68511, H75818, H80551, H80607, N41005, N45017, N56601, N70611, N74891, N93043, N93044, N94350, N98497, W04932, W21511, W21512, W24020, W31043, W47411, W47607, W47659, W47660, W48851, W48618, W52281, W56619, W56649, W68334, W68375, W70156, W70195, W84467, W84552, W90400, W94826, W96342, W96343, N91167, AA016293, AA017674, AA025151, AA025152, AA027955, AA031264, AA031395, AA031855, AA031854, AA035782, AA037318, AA040025, AA056359, AA069269, AA069418, AA069509, AA101608, AA114873, AA114837, AA115697, AA133516, AA220968, AA458530, AA460966, AA463596, AA419091, AA428836, AA507951, AA582836, AA640114, AA659114, AA836669, AA903136, AA903220, AA918099, AA928492, AA971856, AA973427, AA994099, A1016016, A1057267, AA069497, AA206877, AA218868, AA284783, AA284712, AA293434, AA293042, AA402851, AA454608, AA496283, AA609652, AA708123, AA757619, AA757695, AA774425, AA774630, AA775465, AA852435, AA852436, AA852604, AA852605, AA868271, AA884190, T03362, A1042345, A1042606, A1066399, A1086541, A1086967, A1091380, A1091725, A1092820, A1092945, T23722, F03416, F04814, F07127, F08608, F12341
841259	<p>Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1701 of SEQ ID NO:543, b is an integer of 15 to 1715, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:543, and where b is greater than or equal to a + 14.</p>	
841260	<p>Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 3095 of SEQ ID NO:544, b is an integer of 15 to 3109, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:544, and where b is greater than or equal to a + 14.</p>	T93673, R01175, R01287, R72262, R72263, H53584, H53905, N57686, N59657, N63715, N98804, W86302, W86653, W87312, AA055614, AA058962, AA058961, AA149239, AA180323, AA460554, AA460555, AA492261, AA596073, AA604012, AA612811, AA617927, AA631804, AA767954, AA769298, AA804811, AA814647, AA833776, AA872768, AA873458, AA876551, AA886069,

		AA932445, AA976417, AA989268, AI055853, D80933, AI088938, AI096484, AA215901, AA393250, AA435612, AA449044, AA449758, AA653318, AA678103, AA678744, AA705036, AA854081, AA789188, AA813062, AA868902, AI023192, AI033456, AI090508, Z28555, T25877, D30980, D31048, D31377, F00724, AA682530, AA694353
841264	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1162 of SEQ ID NO:545, b is an integer of 15 to 1176, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:545, and where b is greater than or equal to a + 14.	
841275	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1721 of SEQ ID NO:546, b is an integer of 15 to 1735, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:546, and where b is greater than or equal to a + 14.	
841311	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1034 of SEQ ID NO:547, b is an integer of 15 to 1048, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:547, and where b is greater than or equal to a + 14.	
841313	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 722 of SEQ ID NO:548, b is an integer of 15 to 736, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:548, and where b is greater than or equal to a + 14.	
841317	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2217 of SEQ ID NO:549, b is an integer of 15 to 2231, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:549, and where b is greater than or equal to a + 14.	T78127, R31279, R31890, R38014, R68187, R68186, R68960, R81444, R81647, H03085, H42975, N22228, N35405, N40226, N52138, N66461, N66470, W48764, W49783, W58388, AA044222, AA044341, AA131687, AA131731, AA224224, AA224527, AA469092, AA580878, AA573581, AA863153, AA903745, AA971415, C03879, AA249392, AA448556, AA449703, F22605, AA723322, AA904943, Z18868, AA971554, AA991799, AI015846, AI037913, AI056007, AI082497, AI090170, AI095394

841322	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1802 of SEQ ID NO:550, b is an integer of 15 to 1816, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:550, and where b is greater than or equal to a + 14.	R21970, R83459, H65911, W76286, AA182592, AA281797, AA281874, AA291943, H65824, AA580660, AA748474, AA829390, AA293389, AA401755, AA910004, AA994494, A1005165, A1081877
841331	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2596 of SEQ ID NO:551, b is an integer of 15 to 2610, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:551, and where b is greater than or equal to a + 14.	
841332	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 4007 of SEQ ID NO:552, b is an integer of 15 to 4021, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:552, and where b is greater than or equal to a + 14.	
841338	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1766 of SEQ ID NO:553, b is an integer of 15 to 1780, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:553, and where b is greater than or equal to a + 14.	
841345	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 3699 of SEQ ID NO:554, b is an integer of 15 to 3713, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:554, and where b is greater than or equal to a + 14.	
841349	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1983 of SEQ ID NO:555, b is an integer of 15 to 1997, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:555, and where b is greater than or equal to a + 14.	
841355	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 892 of SEQ ID NO:556, b is an integer of 15 to 906, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:556, and where b is greater than or equal to a + 14.	
841417	Preferably excluded from the present invention are	



	one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 3470 of SEQ ID NO:557, b is an integer of 15 to 3484, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:557, and where b is greater than or equal to a + 14.	
841548	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 776 of SEQ ID NO:558, b is an integer of 15 to 790, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:558, and where b is greater than or equal to a + 14.	AA223588
841632	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 544 of SEQ ID NO:559, b is an integer of 15 to 558, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:559, and where b is greater than or equal to a + 14.	
841662	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 520 of SEQ ID NO:560, b is an integer of 15 to 534, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:560, and where b is greater than or equal to a + 14.	H115850, H99706, N78646, W74702, W94916, AA809695
841771	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 3029 of SEQ ID NO:561, b is an integer of 15 to 3043, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:561, and where b is greater than or equal to a + 14.	T50029, T67900, T74699, T74819, T88802, T81298, T84439, T95656, R06092, R06196, R14563, R14966, R14970, R16465, R38948, R40957, R40957, R63975, R64085, R66362, R66363, R67505, H17644, H17758, R92097, H48240, H48331, H49625, H49715, H61167, H62068, H69147, N25753, N36472, N69035, N71493, N92970, N98567, N99536, W00665, W24251, W40582, W45462, W45538, W45525, W45687, W44315, W57971, W57944, W70012, W70013, W86733, AA044684, AA071192, AA071199, AA190325, AA191520, AA533197, AA558210, AA581106, AA581161, AA577119, AA857551, AA878885, AA936839, AA975697, D78980, W28535, C02075, C17857
841827	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1372 of SEQ ID NO:562, b is an integer of 15 to 1386, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:562, and where b is	

	greater than or equal to $a + 14$ .	
841835	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2624 of SEQ ID NO:563, b is an integer of 15 to 2638, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:563, and where b is greater than or equal to $a + 14$ .	
842259	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 677 of SEQ ID NO:564, b is an integer of 15 to 691, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:564, and where b is greater than or equal to $a + 14$ .	
842463	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1953 of SEQ ID NO:565, b is an integer of 15 to 1967, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:565, and where b is greater than or equal to $a + 14$ .	
842595	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1320 of SEQ ID NO:566, b is an integer of 15 to 1334, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:566, and where b is greater than or equal to $a + 14$ .	
842722	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1596 of SEQ ID NO:567, b is an integer of 15 to 1610, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:567, and where b is greater than or equal to $a + 14$ .	
842815	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1398 of SEQ ID NO:568, b is an integer of 15 to 1412, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:568, and where b is greater than or equal to $a + 14$ .	
842818	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1111 of SEQ ID NO:569, b is an integer of 15 to 1125, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:569, and where b is greater than or equal to $a + 14$ .	

843251	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1902 of SEQ ID NO:570, b is an integer of 15 to 1916, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:570, and where b is greater than or equal to a + 14.	
843422	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1239 of SEQ ID NO:571, b is an integer of 15 to 1253, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:571, and where b is greater than or equal to a + 14.	
843784	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1999 of SEQ ID NO:572, b is an integer of 15 to 2013, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:572, and where b is greater than or equal to a + 14.	
844017	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 655 of SEQ ID NO:573, b is an integer of 15 to 669, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:573, and where b is greater than or equal to a + 14.	AA075932
844138	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2418 of SEQ ID NO:574, b is an integer of 15 to 2432, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:574, and where b is greater than or equal to a + 14.	T54096, T54187, T54360, T39143, T40432, T90493, T90589, T89428, T89794, T80000, R00221, R00327, R25952, R26450, R26761, R28459, R55293, R55390, R73233, H42630, H44454, H44498, R83525, R86282, H85785, N33586, N34419, N36244, N48653, N49430, W51915, AA055530, AA055939, AA069732, AA100817, AA122084, AA121407, AA126332, AA133329, AA134151, AA134152, AA134714, AA136470, AA136960, AA157850, AA157906, AA157976, AA159365, AA171854, AA187219, AA186342, AA250818, AA464565, AA464666, AA428826, AA429361, AA491863, AA505512, AA524490, AA558038, AA581979, AA588712, AA593885, AA601110, AA573930, AA577156, AA578735, AA689519, AA730155, AA768486, AA805061, AA826981, AA865985, AA931167, AA947324, AA953202, AA961105, AA962413, AA976440, AA977760, AI032134, AI053416, AI053575,

		AI054013, AI054146, AI054281, U46376, W22126, C00371, C05283, AA641416, AA643346, AA292261, AA421818, AA496452, AA496521, AA653437, AA664399, AA680123, AA431832, AA434143, AA678582, AA705952, AA679763, AA733019, AA781645, AA813232, AA833597, AA844624, AI024151, AI038232, AI042551, AI080152, AI086490, T24101, F03522, F07244
844166	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1358 of SEQ ID NO:575, b is an integer of 15 to 1372, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:575, and where b is greater than or equal to a + 14.	
844194	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2006 of SEQ ID NO:576, b is an integer of 15 to 2020, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:576, and where b is greater than or equal to a + 14.	
844394	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 3147 of SEQ ID NO:577, b is an integer of 15 to 3161, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:577, and where b is greater than or equal to a + 14.	
844450	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2032 of SEQ ID NO:578, b is an integer of 15 to 2046, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:578, and where b is greater than or equal to a + 14.	
844534	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 288 of SEQ ID NO:579, b is an integer of 15 to 302, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:579, and where b is greater than or equal to a + 14.	
844535	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 3053 of SEQ ID NO:580, b is an integer of 15 to 3067, where both a and b correspond to the positions of nucleotide	

	residues shown in SEQ ID NO:580, and where b is greater than or equal to $a + 14$ .	
844644	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1560 of SEQ ID NO:581, b is an integer of 15 to 1574, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:581, and where b is greater than or equal to $a + 14$ .	
844653	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 946 of SEQ ID NO:582, b is an integer of 15 to 960, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:582, and where b is greater than or equal to $a + 14$ .	
844659	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 527 of SEQ ID NO:583, b is an integer of 15 to 541, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:583, and where b is greater than or equal to $a + 14$ .	
844796	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2954 of SEQ ID NO:584, b is an integer of 15 to 2968, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:584, and where b is greater than or equal to $a + 14$ .	
844812	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2594 of SEQ ID NO:585, b is an integer of 15 to 2608, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:585, and where b is greater than or equal to $a + 14$ .	
844894	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1879 of SEQ ID NO:586, b is an integer of 15 to 1893, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:586, and where b is greater than or equal to $a + 14$ .	
845361	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2449 of SEQ ID NO:587, b is an integer of 15 to 2463, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:587, and where b is	T93072, T93161, T69748, T70732, R01200, R01312, R05457, R05477, R05584, R43190, R43190, R65942, R75719, R78234, H03875, H03876, H15845, H16155, H17787, H40269, H45881, R84787, R92493, R92931, H58301, H58912, H58913, H62257,

	greater than or equal to a + 14.	H67051, H68135, H81385, H83681, H91363, H96711, N20348, N22509, N27952, N28616, N31997, N32005, N36007, N39356, N40718, N70011, N70094, N92576, N99870, W00896, W00925, W04623, W25220, W31522, W37278, W37791, W38868, W52654, W51751, AA017158, AA019458, AA022914, AA022915, AA037370, AA037502, AA045696, AA045697, AA046013, AA054565, AA054625, AA069778, AA079736, AA081087, AA081144, AA100055, AA100504, AA100334, AA115581, AA115554, AA126149, AA126373, AA133101, AA130558, AA136439, AA151673, AA151821, AA151822, AA159031, AA165200, AA165201, AA176477, AA176498, AA176771, AA176830, AA182601, AA176736, AA187943, AA188578, AA188675, AA190342, AA190343, AA195091, AA213662, AA213715, AA232222, AA426516, AA424760, AA483564, AA490859, AA491042, AA505249, AA507988, AA508858, AA513433, AA514771, AA514785, AA514980, AA527545, AA534100, AA554008, AA557148, AA584946, AA586481, AA587849, AA588781, AA593916, AA605049, AA604893, AA617650, AA568567, AA621979, AA627588, AA578585, AA578744, AA661910, AA729355, AA729902, AA736994, AA738388, AA740375, AA741213, AA760943, AA830401, AA834201, AA834208, AA834250, AA864864, AA888527, AA906940, AA922073, AA927272, AA931625, AA933055, AA932772, AA936861, AA938504, AA975187, AA977857, AA975594, AI000724, AI014600, AI017381, AI066441, D82733, U47688, N83708, N83790, N85010, W22533, W23255, N86314, N87393, N88971, AA642249, AA642903, AA090403, AA091011, AA095990, AA205824, AA204931, AA643262, AA648446, AA216706, AA219615, AA249170, C75338, AA599187, AA668746, AA670340, AA405611, AA405150, AA708635, AA716044, AA722076, AA722829, AA725716, AA781064, AA844379, AI037987, AI039577, AI078722, AI077655, AI080306, AI084320, AI085219, AI093296, AI093479, AI095168, AI095267, D29018, F02782,
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		F06502, F00762, F00966
845620	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1931 of SEQ ID NO:588, b is an integer of 15 to 1945, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:588, and where b is greater than or equal to a + 14.	
845639	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 802 of SEQ ID NO:589, b is an integer of 15 to 816, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:589, and where b is greater than or equal to a + 14.	
845660	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2293 of SEQ ID NO:590, b is an integer of 15 to 2307, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:590, and where b is greater than or equal to a + 14.	
845720	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1424 of SEQ ID NO:591, b is an integer of 15 to 1438, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:591, and where b is greater than or equal to a + 14.	
845785	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1064 of SEQ ID NO:592, b is an integer of 15 to 1078, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:592, and where b is greater than or equal to a + 14.	
845897	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2478 of SEQ ID NO:593, b is an integer of 15 to 2492, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:593, and where b is greater than or equal to a + 14.	
845922	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1890 of SEQ ID NO:594, b is an integer of 15 to 1904, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:594, and where b is greater than or equal to a + 14.	

846016	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 323 of SEQ ID NO:595, b is an integer of 15 to 337, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:595, and where b is greater than or equal to a + 14.	
846040	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1274 of SEQ ID NO:596, b is an integer of 15 to 1288, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:596, and where b is greater than or equal to a + 14.	
846073	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1038 of SEQ ID NO:597, b is an integer of 15 to 1052, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:597, and where b is greater than or equal to a + 14.	T83567, T83771, R51147, N26938, N32715, N36666, W57781, W74108, AA082091, AA425613
846257	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2079 of SEQ ID NO:598, b is an integer of 15 to 2093, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:598, and where b is greater than or equal to a + 14.	



*Polynucleotide and Polypeptide Variants*

The present invention is directed to variants of the polynucleotide sequence disclosed in SEQ ID NO:X or the complementary strand thereto, and/or the cDNA sequence contained in a cDNA clone contained in the deposit.

5       The present invention also encompasses variants of the cancer polypeptide sequence disclosed in SEQ ID NO:Y, a polypeptide sequence encoded by the polynucleotide sequence in SEQ ID NO:X, and/or a polypeptide sequence encoded by the cDNA in the related cDNA clone contained in the deposit.

10       "Variant" refers to a polynucleotide or polypeptide differing from the polynucleotide or polypeptide of the present invention, but retaining essential properties thereof. Generally, variants are overall closely similar, and, in many regions, identical to the polynucleotide or polypeptide of the present invention.

15       The present invention is also directed to nucleic acid molecules which comprise, or alternatively consist of, a nucleotide sequence which is at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99% or 100%, identical to, for example, the nucleotide coding sequence in SEQ ID NO:X or the complementary strand thereto, the nucleotide coding sequence of the related cDNA contained in a deposited library or the complementary strand thereto, a nucleotide sequence encoding the polypeptide of SEQ ID NO:Y, a nucleotide sequence encoding a polypeptide sequence encoded by the nucleotide sequence in SEQ ID NO:X, a nucleotide  
20       sequence encoding the polypeptide encoded by the cDNA in the related cDNA contained in a deposited library, and/or polynucleotide fragments of any of these nucleic acid molecules (e.g., those fragments described herein). Polypeptides encoded by these nucleic acid molecules are also encompassed by the invention. In another embodiment, the invention encompasses nucleic acid molecules which comprise or alternatively consist of, a  
25       polynucleotide which hybridizes under stringent hybridization conditions, or alternatively, under low stringency conditions, to the nucleotide coding sequence in SEQ ID NO:X, the nucleotide coding sequence of the related cDNA clone contained in a deposited library, a nucleotide sequence encoding the polypeptide of SEQ ID NO:Y, a nucleotide sequence encoding a polypeptide sequence encoded by the nucleotide sequence in SEQ ID NO:X, a  
30       nucleotide sequence encoding the polypeptide encoded by the cDNA in the related cDNA clone contained in a deposited library, and/or polynucleotide fragments of any of these nucleic acid molecules (e.g., those fragments described herein). Polynucleotides which

hybridize to the complement of these nucleic acid molecules under stringent hybridization conditions or alternatively, under lower stringency conditions, are also encompassed by the invention, as are polypeptides encoded by these polynucleotides.

The present invention is also directed to polypeptides which comprise, or alternatively  
5 consist of, an amino acid sequence which is at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99% or 100% identical to, for example, the polypeptide sequence shown in SEQ ID NO:Y, a polypeptide sequence encoded by the nucleotide sequence in SEQ ID NO:X, a polypeptide sequence encoded by the cDNA in the related cDNA clone contained in a deposited library, and/or polypeptide fragments of any of these polypeptides (e.g., those fragments described  
10 herein). Polynucleotides which hybridize to the complement of the nucleic acid molecules encoding these polypeptides under stringent hybridization conditions, or alternatively, under lower stringency conditions, are also encompassed by the invention, as are polypeptides encoded by these polynucleotides.

By a nucleic acid having a nucleotide sequence at least, for example, 95% "identical"  
15 to a reference nucleotide sequence of the present invention, it is intended that the nucleotide sequence of the nucleic acid is identical to the reference sequence except that the nucleotide sequence may include up to five point mutations per each 100 nucleotides of the reference nucleotide sequence encoding the polypeptide. In other words, to obtain a nucleic acid having a nucleotide sequence at least 95% identical to a reference nucleotide sequence, up to  
20 5% of the nucleotides in the reference sequence may be deleted or substituted with another nucleotide, or a number of nucleotides up to 5% of the total nucleotides in the reference sequence may be inserted into the reference sequence. The query sequence may be, for example, an entire sequence referred to in Table 1, an ORF (open reading frame), or any fragment specified as described herein.

25 As a practical matter, whether any particular nucleic acid molecule or polypeptide is at least 80%, 85%, 90%, 95%, 96%, 97%, 98% or 99% identical to a nucleotide sequence of the present invention can be determined conventionally using known computer programs. A preferred method for determining the best overall match between a query sequence (a sequence of the present invention) and a subject sequence, also referred to as a global  
30 sequence alignment, can be determined using the FASTDB computer program based on the algorithm of Brutlag et al. (Comp. App. Biosci. 6:237-245 (1990)). In a sequence alignment the query and subject sequences are both DNA sequences. An RNA sequence can be

compared by converting U's to T's. The result of said global sequence alignment is in percent identity. Preferred parameters used in a FASTDB alignment of DNA sequences to calculate percent identity are: Matrix=Unitary, k-tuple=4, Mismatch Penalty=1, Joining Penalty=30, Randomization Group Length=0, Cutoff Score=1, Gap Penalty=5, Gap Size  
5 Penalty 0.05, Window Size=500 or the length of the subject nucleotide sequence, whichever is shorter.

If the subject sequence is shorter than the query sequence because of 5' or 3' deletions, not because of internal deletions, a manual correction must be made to the results. This is because the FASTDB program does not account for 5' and 3' truncations of the  
10 subject sequence when calculating percent identity. For subject sequences truncated at the 5' or 3' ends, relative to the query sequence, the percent identity is corrected by calculating the number of bases of the query sequence that are 5' and 3' of the subject sequence, which are not matched/aligned, as a percent of the total bases of the query sequence. Whether a nucleotide is matched/aligned is determined by results of the FASTDB sequence alignment.  
15 This percentage is then subtracted from the percent identity, calculated by the above FASTDB program using the specified parameters, to arrive at a final percent identity score. This corrected score is what is used for the purposes of the present invention. Only bases outside the 5' and 3' bases of the subject sequence, as displayed by the FASTDB alignment, which are not matched/aligned with the query sequence, are calculated for the purposes of  
20 manually adjusting the percent identity score.

For example, a 90 base subject sequence is aligned to a 100 base query sequence to determine percent identity. The deletions occur at the 5' end of the subject sequence and therefore, the FASTDB alignment does not show a matched/alignment of the first 10 bases at  
25 5' end. The 10 unpaired bases represent 10% of the sequence (number of bases at the 5' and 3' ends not matched/total number of bases in the query sequence) so 10% is subtracted from the percent identity score calculated by the FASTDB program. If the remaining 90 bases were perfectly matched the final percent identity would be 90%. In another example, a 90 base subject sequence is compared with a 100 base query sequence. This time the deletions are internal deletions so that there are no bases on the 5' or 3' of the subject sequence which  
30 are not matched/aligned with the query. In this case the percent identity calculated by FASTDB is not manually corrected. Once again, only bases 5' and 3' of the subject sequence which are not matched/aligned with the query sequence are manually corrected for. No other

manual corrections are to made for the purposes of the present invention.

By a polypeptide having an amino acid sequence at least, for example, 95% "identical" to a query amino acid sequence of the present invention, it is intended that the amino acid sequence of the subject polypeptide is identical to the query sequence except that  
5 the subject polypeptide sequence may include up to five amino acid alterations per each 100 amino acids of the query amino acid sequence. In other words, to obtain a polypeptide having an amino acid sequence at least 95% identical to a query amino acid sequence, up to 5% of the amino acid residues in the subject sequence may be inserted, deleted, (indels) or substituted with another amino acid. These alterations of the reference sequence may occur  
10 at the amino or carboxy terminal positions of the reference amino acid sequence or anywhere between those terminal positions, interspersed either individually among residues in the reference sequence or in one or more contiguous groups within the reference sequence.

As a practical matter, whether any particular polypeptide is at least 80%, 85%, 90%, 95%, 96%, 97%, 98% or 99% identical to, for instance, the amino acid sequence in SEQ ID  
15 NO:Y or a fragment thereof, the amino acid sequence encoded by the nucleotide sequence in SEQ ID NO:X or a fragment thereof, or the amino acid sequence encoded by the cDNA in the related cDNA clone contained in a deposited library, or a fragment thereof, can be determined conventionally using known computer programs. A preferred method for determining the best overall match between a query sequence (a sequence of the present  
20 invention) and a subject sequence, also referred to as a global sequence alignment, can be determined using the FASTDB computer program based on the algorithm of Brutlag et al. (Comp. App. Biosci.6:237- 245(1990)). In a sequence alignment the query and subject sequences are either both nucleotide sequences or both amino acid sequences. The result of said global sequence alignment is in percent identity. Preferred parameters used in a  
25 FASTDB amino acid alignment are: Matrix=PAM 0, k-tuple=2, Mismatch Penalty=1, Joining Penalty=20, Randomization Group Length=0, Cutoff Score=1, Window Size=sequence length, Gap Penalty=5, Gap Size Penalty=0.05, Window Size=500 or the length of the subject amino acid sequence, whichever is shorter.

If the subject sequence is shorter than the query sequence due to N- or C-terminal  
30 deletions, not because of internal deletions, a manual correction must be made to the results. This is because the FASTDB program does not account for N- and C-terminal truncations of the subject sequence when calculating global percent identity. For subject sequences

truncated at the N- and C-termini, relative to the query sequence, the percent identity is corrected by calculating the number of residues of the query sequence that are N- and C-terminal of the subject sequence, which are not matched/aligned with a corresponding subject residue, as a percent of the total bases of the query sequence. Whether a residue is  
5 matched/aligned is determined by results of the FASTDB sequence alignment. This percentage is then subtracted from the percent identity, calculated by the above FASTDB program using the specified parameters, to arrive at a final percent identity score. This final percent identity score is what is used for the purposes of the present invention. Only residues to the N- and C-termini of the subject sequence, which are not matched/aligned with the  
10 query sequence, are considered for the purposes of manually adjusting the percent identity score. That is, only query residue positions outside the farthest N- and C- terminal residues of the subject sequence.

For example, a 90 amino acid residue subject sequence is aligned with a 100 residue query sequence to determine percent identity. The deletion occurs at the N-terminus of the  
15 subject sequence and therefore, the FASTDB alignment does not show a matching/alignment of the first 10 residues at the N-terminus. The 10 unpaired residues represent 10% of the sequence (number of residues at the N- and C- termini not matched/total number of residues in the query sequence) so 10% is subtracted from the percent identity score calculated by the FASTDB program. If the remaining 90 residues were perfectly matched the final percent  
20 identity would be 90%. In another example, a 90 residue subject sequence is compared with a 100 residue query sequence. This time the deletions are internal deletions so there are no residues at the N- or C-termini of the subject sequence which are not matched/aligned with the query. In this case the percent identity calculated by FASTDB is not manually corrected. Once again, only residue positions outside the N- and C-terminal ends of the subject  
25 sequence, as displayed in the FASTDB alignment, which are not matched/aligned with the query sequence are manually corrected for. No other manual corrections are to made for the purposes of the present invention.

The variants may contain alterations in the coding regions, non-coding regions, or both. Especially preferred are polynucleotide variants containing alterations which produce  
30 silent substitutions, additions, or deletions, but do not alter the properties or activities of the encoded polypeptide. Nucleotide variants produced by silent substitutions due to the degeneracy of the genetic code are preferred. Moreover, variants in which less than 50, less

than 40, less than 30, less than 20, less than 10, or 5-50, 5-25, 5-10, 1-5, or 1-2 amino acids are substituted, deleted, or added in any combination are also preferred. Polynucleotide variants can be produced for a variety of reasons, e.g., to optimize codon expression for a particular host (change codons in the human mRNA to those preferred by a bacterial host such as *E. coli*).

Naturally occurring variants are called "allelic variants," and refer to one of several alternate forms of a gene occupying a given locus on a chromosome of an organism. (Genes II, Lewin, B., ed., John Wiley & Sons, New York (1985).) These allelic variants can vary at either the polynucleotide and/or polypeptide level and are included in the present invention.

Alternatively, non-naturally occurring variants may be produced by mutagenesis techniques or by direct synthesis.

Using known methods of protein engineering and recombinant DNA technology, variants may be generated to improve or alter the characteristics of the polypeptides of the present invention. For instance, as discussed herein, one or more amino acids can be deleted from the N-terminus or C-terminus of the polypeptide of the present invention without substantial loss of biological function. The authors of Ron et al., *J. Biol. Chem.* 268: 2984-2988 (1993), reported variant KGF proteins having heparin binding activity even after deleting 3, 8, or 27 amino-terminal amino acid residues. Similarly, Interferon gamma exhibited up to ten times higher activity after deleting 8-10 amino acid residues from the carboxy terminus of this protein. (Dobeli et al., *J. Biotechnology* 7:199-216 (1988).)

Moreover, ample evidence demonstrates that variants often retain a biological activity similar to that of the naturally occurring protein. For example, Gayle and coworkers (*J. Biol. Chem.* 268:22105-22111 (1993)) conducted extensive mutational analysis of human cytokine IL-1a. They used random mutagenesis to generate over 3,500 individual IL-1a mutants that averaged 2.5 amino acid changes per variant over the entire length of the molecule. Multiple mutations were examined at every possible amino acid position. The investigators found that "[m]ost of the molecule could be altered with little effect on either [binding or biological activity]." (See, Abstract.) In fact, only 23 unique amino acid sequences, out of more than 3,500 nucleotide sequences examined, produced a protein that significantly differed in activity from wild-type.

Furthermore, as discussed herein, even if deleting one or more amino acids from the N-terminus or C-terminus of a polypeptide results in modification or loss of one or more

biological functions, other biological activities may still be retained. For example, the ability of a deletion variant to induce and/or to bind antibodies which recognize the secreted form will likely be retained when less than the majority of the residues of the secreted form are removed from the N-terminus or C-terminus. Whether a particular polypeptide lacking N- or C-terminal residues of a protein retains such immunogenic activities can readily be determined by routine methods described herein and otherwise known in the art.

Thus, the invention further includes polypeptide variants which show a functional activity (e.g., biological activity) of the polypeptide of the invention of which they are a variant. Such variants include deletions, insertions, inversions, repeats, and substitutions selected according to general rules known in the art so as have little effect on activity.

The present application is directed to nucleic acid molecules at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99% or 100% identical to the nucleic acid sequences disclosed herein or fragments thereof, (e.g., including but not limited to fragments encoding a polypeptide having the amino acid sequence of an N and/or C terminal deletion), irrespective of whether they encode a polypeptide having functional activity. This is because even where a particular nucleic acid molecule does not encode a polypeptide having functional activity, one of skill in the art would still know how to use the nucleic acid molecule, for instance, as a hybridization probe or a polymerase chain reaction (PCR) primer. Uses of the nucleic acid molecules of the present invention that do not encode a polypeptide having functional activity include, inter alia, (1) isolating a gene or allelic or splice variants thereof in a cDNA library; (2) in situ hybridization (e.g., "FISH") to metaphase chromosomal spreads to provide precise chromosomal location of the gene, as described in Verma et al., Human Chromosomes: A Manual of Basic Techniques, Pergamon Press, New York (1988); and (3) Northern Blot analysis for detecting mRNA expression in specific tissues.

Preferred, however, are nucleic acid molecules having sequences at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99% or 100% identical to the nucleic acid sequences disclosed herein, which do, in fact, encode a polypeptide having a functional activity of a polypeptide of the invention.

Of course, due to the degeneracy of the genetic code, one of ordinary skill in the art will immediately recognize that a large number of the nucleic acid molecules having a sequence at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identical to, for example, the nucleic acid sequence of the cDNA in the related cDNA clone contained in a

deposited library, the nucleic acid sequence referred to in Table I (SEQ ID NO:X), or fragments thereof, will encode polypeptides "having functional activity." In fact, since degenerate variants of any of these nucleotide sequences all encode the same polypeptide, in many instances, this will be clear to the skilled artisan even without performing the above described comparison assay. It will be further recognized in the art that, for such nucleic acid molecules that are not degenerate variants, a reasonable number will also encode a polypeptide having functional activity. This is because the skilled artisan is fully aware of amino acid substitutions that are either less likely or not likely to significantly effect protein function (e.g., replacing one aliphatic amino acid with a second aliphatic amino acid), as further described below.

For example, guidance concerning how to make phenotypically silent amino acid substitutions is provided in Bowie et al., "Deciphering the Message in Protein Sequences: Tolerance to Amino Acid Substitutions," *Science* 247:1306-1310 (1990), wherein the authors indicate that there are two main strategies for studying the tolerance of an amino acid sequence to change.

The first strategy exploits the tolerance of amino acid substitutions by natural selection during the process of evolution. By comparing amino acid sequences in different species, conserved amino acids can be identified. These conserved amino acids are likely important for protein function. In contrast, the amino acid positions where substitutions have been tolerated by natural selection indicates that these positions are not critical for protein function. Thus, positions tolerating amino acid substitution could be modified while still maintaining biological activity of the protein.

The second strategy uses genetic engineering to introduce amino acid changes at specific positions of a cloned gene to identify regions critical for protein function. For example, site directed mutagenesis or alanine-scanning mutagenesis (introduction of single alanine mutations at every residue in the molecule) can be used. (Cunningham and Wells, *Science* 244:1081-1085 (1989).) The resulting mutant molecules can then be tested for biological activity.

As the authors state, these two strategies have revealed that proteins are surprisingly tolerant of amino acid substitutions. The authors further indicate which amino acid changes are likely to be permissive at certain amino acid positions in the protein. For example, most buried (within the tertiary structure of the protein) amino acid residues require nonpolar side



chains, whereas few features of surface side chains are generally conserved. Moreover, tolerated conservative amino acid substitutions involve replacement of the aliphatic or hydrophobic amino acids Ala, Val, Leu and Ile; replacement of the hydroxyl residues Ser and Thr; replacement of the acidic residues Asp and Glu; replacement of the amide residues Asn and Gln, replacement of the basic residues Lys, Arg, and His; replacement of the aromatic residues Phe, Tyr, and Trp, and replacement of the small-sized amino acids Ala, Ser, Thr, Met, and Gly. Besides conservative amino acid substitution, variants of the present invention include (i) substitutions with one or more of the non-conserved amino acid residues, where the substituted amino acid residues may or may not be one encoded by the genetic code, or (ii) substitution with one or more of amino acid residues having a substituent group, or (iii) fusion of the mature polypeptide with another compound, such as a compound to increase the stability and/or solubility of the polypeptide (for example, polyethylene glycol), or (iv) fusion of the polypeptide with additional amino acids, such as, for example, an IgG Fc fusion region peptide, or leader or secretory sequence, or a sequence facilitating purification. Such variant polypeptides are deemed to be within the scope of those skilled in the art from the teachings herein.

For example, polypeptide variants containing amino acid substitutions of charged amino acids with other charged or neutral amino acids may produce proteins with improved characteristics, such as less aggregation. Aggregation of pharmaceutical formulations both reduces activity and increases clearance due to the aggregate's immunogenic activity. (Pinckard et al., Clin. Exp. Immunol. 2:331-340 (1967); Robbins et al., Diabetes 36: 838-845 (1987); Cleland et al., Crit. Rev. Therapeutic Drug Carrier Systems 10:307-377 (1993).)

A further embodiment of the invention relates to a polypeptide which comprises the amino acid sequence of a polypeptide having an amino acid sequence which contains at least one amino acid substitution, but not more than 50 amino acid substitutions, even more preferably, not more than 40 amino acid substitutions, still more preferably, not more than 30 amino acid substitutions, and still even more preferably, not more than 20 amino acid substitutions. Of course it is highly preferable for a polypeptide to have an amino acid sequence which comprises the amino acid sequence of a polypeptide of SEQ ID NO:Y, an amino acid sequence encoded by SEQ ID NO:X, and/or the amino acid sequence encoded by the cDNA in the related cDNA clone contained in a deposited library which contains, in order of ever-increasing preference, at least one, but not more than 10, 9, 8, 7, 6, 5, 4, 3, 2 or 1

amino acid substitutions. In specific embodiments, the number of additions, substitutions, and/or deletions in the amino acid sequence of SEQ ID NO:Y or fragments thereof (e.g., the mature form and/or other fragments described herein), an amino acid sequence encoded by SEQ ID NO:X or fragments thereof, and/or the amino acid sequence encoded by the cDNA in the related cDNA clone contained in a deposited library or fragments thereof, is 1-5, 5-10, 5-25, 5-50, 10-50 or 50-150, conservative amino acid substitutions are preferable.

#### *Polynucleotide and Polypeptide Fragments*

The present invention is also directed to polynucleotide fragments of the cancer polynucleotides (nucleic acids) of the invention. In the present invention, a "polynucleotide fragment" refers, for example, to a polynucleotide having a nucleic acid sequence which: is a portion of the cDNA contained in a deposited cDNA clone; or is a portion of a polynucleotide sequence encoding the polypeptide encoded by the cDNA contained in a deposited cDNA clone; or is a portion of the polynucleotide sequence in SEQ ID NO:X or the complementary strand thereto; or is a polynucleotide sequence encoding a portion of the polypeptide of SEQ ID NO:Y; or is a polynucleotide sequence encoding a portion of a polypeptide encoded by SEQ ID NO:X or the complementary strand thereto. The nucleotide fragments of the invention are preferably at least about 15 nt, and more preferably at least about 20 nt, still more preferably at least about 30 nt, and even more preferably, at least about 40 nt, at least about 50 nt, at least about 75 nt, at least about 100 nt, at least about 125 nt or at least about 150 nt in length. A fragment "at least 20 nt in length," for example, is intended to include 20 or more contiguous bases from, for example, the sequence contained in the cDNA in a related cDNA clone contained in a deposited library, the nucleotide sequence shown in SEQ ID NO:X or the complementary stand thereto. In this context "about" includes the particularly recited value or a value larger or smaller by several (5, 4, 3, 2, or 1) nucleotides. These nucleotide fragments have uses that include, but are not limited to, as diagnostic probes and primers as discussed herein. Of course, larger fragments (e.g., at least 150, 175, 200, 250, 500, 600, 1000, or 2000 nucleotides in length) are also encompassed by the invention.

Moreover, representative examples of polynucleotide fragments of the invention, include, for example, fragments comprising, or alternatively consisting of, a sequence from about nucleotide number 1-50, 51-100, 101-150, 151-200, 201-250, 251-300, 301-350, 351-400, 401-450, 451-500, 501-550, 551-600, 651-700, 701-750, 751-800, 800-850, 851-900,

901-950, 951-1000, 1001-1050, 1051-1100, 1101-1150, 1151-1200, 1201-1250, 1251-1300, 1301-1350, 1351-1400, 1401-1450, 1451-1500, 1501-1550, 1551-1600, 1601-1650, 1651-1700, 1701-1750, 1751-1800, 1801-1850, 1851-1900, 1901-1950, 1951-2000, 2001-2050, 2051-2100, 2101-2150, 2151-2200, 2201-2250, 2251-2300, 2301-2350, 2351-2400, 2401-2450, 2451-2500, 2501-2550, 2551-2600, 2601-2650, 2651-2700, 2701-2750, 2751-2800, 2801-2850, 2851-2900, 2901-2950, 2951-3000, 3001-3050, 3051-3100, 3101-3150, 3151-3200, 3201-3250, 3251-3300, 3301-3350, 3351-3400, 3401-3450, 3451-3500, 3501-3550, and 3551 to the end of SEQ ID NO:X, or the complementary strand thereto. In this context “about” includes the particularly recited range or a range larger or smaller by several (5, 4, 3, 2, or 1) nucleotides, at either terminus or at both termini. Preferably, these fragments encode a polypeptide which has a functional activity (e.g., biological activity) of the polypeptide encoded by the polynucleotide of which the sequence is a portion. More preferably, these fragments can be used as probes or primers as discussed herein. Polynucleotides which hybridize to one or more of these nucleic acid molecules under stringent hybridization conditions or alternatively, under lower stringency conditions, are also encompassed by the invention, as are polypeptides encoded by these polynucleotides or fragments.

Moreover, representative examples of polynucleotide fragments of the invention, include, for example, fragments comprising, or alternatively consisting of, a sequence from about nucleotide number 1-50, 51-100, 101-150, 151-200, 201-250, 251-300, 301-350, 351-400, 401-450, 451-500, 501-550, 551-600, 651-700, 701-750, 751-800, 800-850, 851-900, 901-950, 951-1000, 1001-1050, 1051-1100, 1101-1150, 1151-1200, 1201-1250, 1251-1300, 1301-1350, 1351-1400, 1401-1450, 1451-1500, 1501-1550, 1551-1600, 1601-1650, 1651-1700, 1701-1750, 1751-1800, 1801-1850, 1851-1900, 1901-1950, 1951-2000, 2001-2050, 2051-2100, 2101-2150, 2151-2200, 2201-2250, 2251-2300, 2301-2350, 2351-2400, 2401-2450, 2451-2500, 2501-2550, 2551-2600, 2601-2650, 2651-2700, 2701-2750, 2751-2800, 2801-2850, 2851-2900, 2901-2950, 2951-3000, 3001-3050, 3051-3100, 3101-3150, 3151-3200, 3201-3250, 3251-3300, 3301-3350, 3351-3400, 3401-3450, 3451-3500, 3501-3550, and 3551 to the end of the cDNA nucleotide sequence contained in the deposited cDNA clone, or the complementary strand thereto. In this context “about” includes the particularly recited range, or a range larger or smaller by several (5, 4, 3, 2, or 1) nucleotides, at either terminus or at both termini. Preferably, these fragments encode a polypeptide which has a functional activity (e.g., biological activity) of the polypeptide encoded by the cDNA

nucleotide sequence contained in the deposited cDNA clone. More preferably, these fragments can be used as probes or primers as discussed herein. Polynucleotides which hybridize to one or more of these fragments under stringent hybridization conditions or alternatively, under lower stringency conditions, are also encompassed by the invention, as are polypeptides encoded by these polynucleotides or fragments.

In the present invention, a "polypeptide fragment" refers to an amino acid sequence which is a portion of that contained in SEQ ID NO:Y, a portion of an amino acid sequence encoded by the polynucleotide sequence of SEQ ID NO:X, and/or encoded by the cDNA contained in the related cDNA clone contained in a deposited library. Protein (polypeptide) fragments may be "free-standing," or comprised within a larger polypeptide of which the fragment forms a part or region, most preferably as a single continuous region. Representative examples of polypeptide fragments of the invention, include, for example, fragments comprising, or alternatively consisting of, an amino acid sequence from about amino acid number 1-20, 21-40, 41-60, 61-80, 81-100, 102-120, 121-140, 141-160, 161-180, 181-200, 201-220, 221-240, 241-260, 261-280, 281-300, 301-320, 321-340, 341-360, 361-380, 381-400, 401-420, 421-440, 441-460, 461-480, 481-500, 501-520, 521-540, 541-560, 561-580, 581-600, 601-620, 621-640, 641-660, 661-680, 681-700, 701-720, 721-740, 741-760, 761-780, 781-800, 801-820, 821-840, 841-860, 861-880, 881-900, 901-920, 921-940, 941-960, 961-980, 981-1000, 1001-1020, 1021-1040, 1041-1060, 1061-1080, 1081-1100, 1101-1120, 1121-1140, 1141-1160, 1161-1180, and 1181 to the end of SEQ ID NO:Y. Moreover, polypeptide fragments of the invention may be at least about 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 100, 110, 120, 130, 140, or 150 amino acids in length. In this context "about" includes the particularly recited ranges or values, or ranges or values larger or smaller by several (5, 4, 3, 2, or 1) amino acids, at either terminus or at both termini. Polynucleotides encoding these polypeptide fragments are also encompassed by the invention.

Even if deletion of one or more amino acids from the N-terminus of a protein results in modification or loss of one or more biological functions of the protein, other functional activities (e.g., biological activities, ability to multimerize, ability to bind a ligand) may still be retained. For example, the ability of shortened muteins to induce and/or bind to antibodies which recognize the complete or mature forms of the polypeptides generally will be retained when less than the majority of the residues of the complete or mature polypeptide are

removed from the N-terminus. Whether a particular polypeptide lacking N-terminal residues of a complete polypeptide retains such immunologic activities can readily be determined by routine methods described herein and otherwise known in the art. It is not unlikely that a mutein with a large number of deleted N-terminal amino acid residues may retain some biological or immunogenic activities. In fact, peptides composed of as few as six amino acid residues may often evoke an immune response.

Accordingly, polypeptide fragments of the invention include the secreted protein as well as the mature form. Further preferred polypeptide fragments include the secreted protein or the mature form having a continuous series of deleted residues from the amino or the carboxy terminus, or both. For example, any number of amino acids, ranging from 1-60, can be deleted from the amino terminus of either the secreted polypeptide or the mature form. Similarly, any number of amino acids, ranging from 1-30, can be deleted from the carboxy terminus of the secreted protein or mature form. Furthermore, any combination of the above amino and carboxy terminus deletions are preferred. Similarly, polynucleotides encoding these polypeptide fragments are also preferred.

The present invention further provides polypeptides having one or more residues deleted from the amino terminus of the amino acid sequence of a polypeptide disclosed herein (e.g., a polypeptide of SEQ ID NO:Y, a polypeptide encoded by the polynucleotide sequence contained in SEQ ID NO:X, and/or a polypeptide encoded by the cDNA contained in the related cDNA clone contained in a deposited library). In particular, N-terminal deletions may be described by the general formula m-q, where q is a whole integer representing the total number of amino acid residues in a polypeptide of the invention (e.g., the polypeptide disclosed in SEQ ID NO:Y), and m is defined as any integer ranging from 2 to q-6. Polynucleotides encoding these polypeptides are also encompassed by the invention.

Also as mentioned above, even if deletion of one or more amino acids from the C-terminus of a protein results in modification or loss of one or more biological functions of the protein, other functional activities (e.g., biological activities, ability to multimerize, ability to bind a ligand) may still be retained. For example the ability of the shortened mutein to induce and/or bind to antibodies which recognize the complete or mature forms of the polypeptide generally will be retained when less than the majority of the residues of the complete or mature polypeptide are removed from the C-terminus. Whether a particular polypeptide lacking C-terminal residues of a complete polypeptide retains such immunologic

activities can readily be determined by routine methods described herein and otherwise known in the art. It is not unlikely that a mutein with a large number of deleted C-terminal amino acid residues may retain some biological or immunogenic activities. In fact, peptides composed of as few as six amino acid residues may often evoke an immune response.

5           Accordingly, the present invention further provides polypeptides having one or more residues from the carboxy terminus of the amino acid sequence of a polypeptide disclosed herein (e.g., a polypeptide of SEQ ID NO:Y, a polypeptide encoded by the polynucleotide sequence contained in SEQ ID NO:X, and/or a polypeptide encoded by the cDNA contained in deposited cDNA clone referenced in Table 1). In particular, C-terminal deletions may be  
10       described by the general formula 1-n, where n is any whole integer ranging from 6 to q-1, and where n corresponds to the position of an amino acid residue in a polypeptide of the invention. Polynucleotides encoding these polypeptides are also encompassed by the invention.

          In addition, any of the above described N- or C-terminal deletions can be combined to  
15       produce a N- and C-terminal deleted polypeptide. The invention also provides polypeptides having one or more amino acids deleted from both the amino and the carboxyl termini, which may be described generally as having residues m-n of a polypeptide encoded by SEQ ID NO:X (e.g., including, but not limited to, the preferred polypeptide disclosed as SEQ ID NO:Y), and/or the cDNA in the related cDNA clone contained in a deposited library, where n  
20       and m are integers as described above. Polynucleotides encoding these polypeptides are also encompassed by the invention.

          Any polypeptide sequence contained in the polypeptide of SEQ ID NO:Y, encoded by the polynucleotide sequences set forth as SEQ ID NO:X, or encoded by the cDNA in the related cDNA clone contained in a deposited library may be analyzed to determine certain  
25       preferred regions of the polypeptide. For example, the amino acid sequence of a polypeptide encoded by a polynucleotide sequence of SEQ ID NO:X, or the cDNA in a deposited cDNA clone may be analyzed using the default parameters of the DNASTAR computer algorithm (DNASTAR, Inc., 1228 S. Park St., Madison, WI 53715 USA; <http://www.dnastar.com/>).

          Polypeptide regions that may be routinely obtained using the DNASTAR computer  
30       algorithm include, but are not limited to, Garnier-Robson alpha-regions, beta-regions, turn-regions, and coil-regions, Chou-Fasman alpha-regions, beta-regions, and turn-regions, Kyte-Doolittle hydrophilic regions and hydrophobic regions, Eisenberg alpha- and

beta-amphipathic regions, Karplus-Schulz flexible regions, Emini surface-forming regions and Jameson-Wolf regions of high antigenic index. Among highly preferred polynucleotides of the invention in this regard are those that encode polypeptides comprising regions that combine several structural features, such as several (e.g., 1, 2, 3 or 4) of the features set out  
5 above.

Additionally, Kyte-Doolittle hydrophilic regions and hydrophobic regions, Emini surface-forming regions, and Jameson-Wolf regions of high antigenic index (i.e., containing four or more contiguous amino acids having an antigenic index of greater than or equal to 1.5, as identified using the default parameters of the Jameson-Wolf program) can routinely be  
10 used to determine polypeptide regions that exhibit a high degree of potential for antigenicity. Regions of high antigenicity are determined from data by DNASTAR analysis by choosing values which represent regions of the polypeptide which are likely to be exposed on the surface of the polypeptide in an environment in which antigen recognition may occur in the process of initiation of an immune response.

15 Preferred polypeptide fragments of the invention are fragments comprising, or alternatively consisting of, an amino acid sequence that displays a functional activity of the polypeptide sequence of which the amino acid sequence is a fragment.

By a polypeptide demonstrating a "functional activity" is meant, a polypeptide capable of displaying one or more known functional activities associated with a full-length  
20 (complete) protein of the invention. Such functional activities include, but are not limited to, biological activity, antigenicity [ability to bind (or compete with a polypeptide for binding) to an anti-polypeptide antibody], immunogenicity (ability to generate antibody which binds to a specific polypeptide of the invention), ability to form multimers with polypeptides of the invention, and ability to bind to a receptor or ligand for a polypeptide.

25 Other preferred polypeptide fragments are biologically active fragments. Biologically active fragments are those exhibiting activity similar, but not necessarily identical, to an activity of the polypeptide of the present invention. The biological activity of the fragments may include an improved desired activity, or a decreased undesirable activity.

In preferred embodiments, polypeptides of the invention comprise, or alternatively  
30 consist of, one, two, three, four, five or more of the antigenic fragments of the polypeptide of SEQ ID NO:Y, or portions thereof. Polynucleotides encoding these polypeptides are also encompassed by the invention.

Table 4.

Sequence/ Contig ID	Epitope
507291	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 843 as residues: Pro-12 to Pro-20, Lys-27 to Gly-34, Pro-67 to Arg-72, Asp-102 to Thr-111, Asp-136 to Gly-142, Ser-153 to Pro-158.
508000	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 844 as residues: Ala-16 to Trp-35.
518325	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 845 as residues: Glu-60 to Asp-67.
523111	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 846 as residues: Ser-1 to Gln-10.
532211	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 848 as residues: Cys-17 to Arg-22.
532247	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 849 as residues: Val-4 to His-10.
537932	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 850 as residues: Ser-62 to Gly-68.
540117	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 851 as residues: Pro-24 to Arg-30, Met-101 to Phe-106, Thr-138 to Asn-153.
547710	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 852 as residues: Asp-1 to Arg-7, Glu-25 to His-31, Ile-51 to Lys-56, Pro-61 to Pro-67, Gly-113 to Thr-119, Lys-125 to Asp-130, His-335 to Gly-340, Arg-364 to Pro-371.
551747	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 853 as residues: Lys-79 to Ala-88, Ser-109 to Leu-125, Asp-155 to Lys-163, Tyr-211 to Thr-219, Pro-221 to Ala-226.
552799	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 854 as residues: Gln-81 to Thr-114, Gln-200 to Arg-206.
553243	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 855 as residues: Ala-43 to Asp-48, Asp-64 to Lys-69, His-88 to Thr-94, Ala-107 to Phe-113, Leu-117 to Ser-125, Thr-132 to Glu-138, Ser-169 to Trp-181, Ser-194 to Thr-200.
553368	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 856 as residues: Ser-52 to Arg-57, Leu-76 to Gly-82, Ser-91 to Glu-96, Tyr-132 to Ala-147.
554349	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 857 as residues: Ala-31 to Gly-36, Ala-68 to Tyr-75, Gln-121 to Asp-127.
558491	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 858 as residues: Pro-1 to Arg-10.
558983	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 859 as residues: Pro-37 to Gly-42, Val-67 to Lys-84, Gln-122 to Gly-127.
589390	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 862 as residues: Glu-14 to Asn-19, Arg-68 to Ser-74, Ser-79 to Ala-84, Lys-95 to Ile-101, Lys-125 to Glu-138.
596882	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 863 as residues: Lys-15 to Lys-23, Pro-29 to Gly-34.
616289	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 864 as residues: Leu-1 to Pro-13, Thr-64 to Gly-70, Lys-119 to Arg-130.
622140	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 865 as residues: Ser-1 to Lys-6, Pro-16 to Ser-23, Arg-49 to Glu-58.
647714	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 867 as residues: Arg-1 to Gly-9, Glu-27 to Gly-36, Pro-72 to Phe-86, Pro-104 to Cys-111, Gln-145 to Lys-162, Arg-226 to Trp-233.
652156	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 871 as residues: Asn-30 to Ile-43, Ile-76 to Lys-81.
653010	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 872 as



	residues: Ser-1 to Ala-10.
655904	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 873 as residues: Ala-21 to Cys-27, Ser-76 to Gly-87, Ser-112 to Trp-121, Trp-128 to Asn-133, Glu-225 to Cys-231, Tyr-238 to Cys-248, Lys-269 to Asp-279, Phe-292 to Thr-298, Cys-357 to Ala-362, Pro-383 to Pro-388, Lys-412 to Lys-420.
657852	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 874 as residues: Arg-10 to Lys-22, Gln-48 to Glu-53, Arg-73 to Asn-86.
666414	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 875 as residues: Asn-9 to Lys-19, Arg-27 to Gly-32, Ser-58 to Thr-70, Ala-81 to Pro-86.
670188	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 877 as residues: Asn-68 to Ser-75.
670279	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 878 as residues: Lys-86 to Lys-91, Glu-101 to Val-120, Ala-130 to Glu-136.
670729	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 879 as residues: Ala-116 to Asp-134.
676496	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 881 as residues: Ile-1 to Arg-8.
678248	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 883 as residues: Ala-16 to Lys-22, Tyr-30 to Asn-35, Asp-61 to Val-70, Arg-129 to Asn-135, Thr-142 to Gly-148.
683668	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 884 as residues: Ser-3 to Gly-28, Gly-46 to Pro-56, Gly-70 to Ile-92, Gln-102 to Ser-117, Ala-123 to Pro-129, Pro-135 to Leu-140, Pro-150 to Asp-158, Pro-165 to Pro-177, Gln-188 to Asp-205, Ile-230 to Arg-245, His-251 to Trp-260, Asp-262 to Cys-267, Asn-296 to Arg-307, Glu-322 to Pro-330, Ile-351 to Asn-357, Asp-363 to Leu-369, Glu-386 to Phe-391, Lys-415 to Ser-420.
693172	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 885 as residues: Arg-11 to Arg-18, Pro-51 to Lys-58.
694303	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 886 as residues: Pro-12 to Ser-17, Leu-30 to Cys-39, Val-49 to Pro-54, Pro-67 to Leu-73, Pro-84 to Gln-90, His-99 to Leu-109.
695042	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 887 as residues: Ser-4 to Trp-28, Pro-51 to Leu-56, Asn-64 to His-70.
699799	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 888 as residues: Gln-17 to Phe-25, Glu-42 to Tyr-48, Val-52 to Gly-57, Pro-67 to Ser-73, Thr-97 to Gln-106, Gln-113 to Leu-123, Arg-171 to Asp-178, Arg-184 to Leu-191, Ile-195 to Phe-203, Lys-212 to Glu-217, Ala-236 to Asp-244, Arg-255 to Leu-260, Lys-266 to His-273, Glu-357 to Glu-363.
703015	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 890 as residues: Pro-27 to Asp-37, Gly-55 to Pro-61, His-96 to Ala-101, Glu-151 to Asn-156, Tyr-166 to Cys-178.
706391	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 891 as residues: Pro-22 to Ala-34, Pro-40 to Glu-52.
706924	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 893 as residues: Gly-1 to Gly-9, Gln-21 to Met-27.
707642	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 894 as residues: Glu-33 to Lys-40, Asn-55 to Lys-64, Tyr-104 to Cys-110, Ser-138 to Arg-148, Arg-157 to Gly-163, Lys-165 to Asn-172.
710369	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 895 as residues: Asn-1 to Thr-10.
718826	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 896 as residues: Ser-57 to Pro-63, Lys-93 to Ser-99.
719790	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 897 as residues: Phe-4 to Gln-23, Glu-47 to Ala-56, Asn-95 to Gln-102, Gln-109 to Glu-115, Arg-168 to Glu-175, Thr-196 to Arg-201, Lys-209 to Asp-215, Val-236 to Val-243.
720222	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 898 as

	residues: Glu-37 to Arg-43, Gly-62 to Pro-67, Gly-95 to Val-101, Gln-109 to Asp-114, Ala-137 to Phe-145, Asp-181 to Ser-188.
724033	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 899 as residues: Glu-55 to Glu-60, Asp-76 to Ser-85, Lys-106 to Asp-111, Gln-131 to Arg-137, Ala-172 to Gly-218.
724767	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 900 as residues: Leu-49 to Tyr-56, Tyr-114 to Glu-136, Arg-142 to Gly-148.
727065	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 901 as residues: Asn-41 to Gly-46, Lys-82 to His-88, Glu-107 to His-112, Leu-127 to Asp-132, Phe-163 to Phe-175, Thr-202 to Ile-209, Lys-229 to Gly-237, Ala-239 to Tyr-245.
727246	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 902 as residues: Pro-2 to Gly-10.
739448	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 908 as residues: His-2 to Leu-8, Gln-33 to Glu-40, Ala-44 to Glu-55, Gly-57 to Ser-67, Glu-70 to Ala-84, Glu-95 to Lys-111, Ile-186 to Asp-205, Leu-232 to Asp-238.
740060	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 910 as residues: Pro-44 to Thr-50, Arg-72 to Lys-80, Tyr-241 to Asn-251, Lys-273 to Gly-282, Ser-302 to Asn-312, Pro-337 to Ser-343, Ile-367 to Asp-376, Gly-395 to Tyr-417, Ser-442 to Gln-448.
741560	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 911 as residues: Gln-33 to Tyr-39, Pro-42 to Phe-47.
742543	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 912 as residues: Phe-10 to Tyr-15, Glu-139 to Asp-144, Glu-166 to Asn-171, Lys-175 to Glu-181.
742831	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 913 as residues: Val-64 to Glu-69.
745327	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 914 as residues: Arg-1 to Pro-13, Pro-54 to Ala-61.
745695	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 915 as residues: Trp-130 to Ser-135, Leu-199 to Thr-210, Ser-221 to Gln-229, Ala-249 to Tyr-255, Pro-257 to Pro-267, Ser-309 to Arg-314.
750316	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 916 as residues: Pro-18 to Asn-24, Thr-65 to Asp-70.
750522	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 917 as residues: Gln-10 to Lys-15.
750583	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 918 as residues: Lys-9 to Thr-15, Gln-32 to Gln-40.
751020	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 919 as residues: Arg-39 to Leu-47, Ser-107 to Ile-117, Pro-135 to Gln-144.
752196	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 920 as residues: Lys-20 to Lys-28.
753084	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 921 as residues: Lys-84 to Thr-98, Arg-128 to Ser-134, Arg-244 to Asn-252, Lys-365 to His-372.
754957	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 922 as residues: Pro-101 to Glu-106, Glu-116 to Asp-127, Ser-199 to Ile-210, Asp-217 to Asp-229, Ser-239 to Gly-244, Gln-262 to Asn-273, Pro-279 to Ser-284, Lys-318 to Arg-326, Lys-334 to Ile-341.
756557	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 923 as residues: Val-13 to Phe-21, Ile-55 to Pro-63, Ser-69 to Leu-74, Arg-82 to Leu-96, Asn-131 to Leu-139, Ile-156 to Thr-164, Thr-241 to Leu-249, Gly-273 to Ser-279, Thr-282 to Arg-289.
756712	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 924 as residues: Ile-4 to Thr-37, Gln-42 to Ser-48, Asn-56 to Lys-69, Ser-79 to Ser-85.
757414	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 925 as residues: Glu-14 to Thr-23, His-50 to Arg-62, Tyr-72 to Cys-78, Gly-121 to Pro-128.

757614	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 926 as residues: Gly-13 to Cys-19, Thr-32 to Glu-38, Val-44 to Gln-53, Lys-55 to Asp-60, Gln-65 to Glu-70, Lys-89 to Glu-105, Glu-112 to Asp-142, Glu-147 to Arg-152, Glu-211 to Leu-216, Leu-227 to Ser-232, Lys-245 to Lys-255, Glu-278 to Tyr-291, Gln-297 to Arg-303.
759878	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 928 as residues: Trp-16 to Glu-21, Trp-45 to Pro-54, Ile-154 to Phe-162, Gly-174 to Leu-181.
760227	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 929 as residues: Arg-99 to Asp-104.
766051	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 931 as residues: Asp-10 to Lys-19.
768053	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 933 as residues: Ile-1 to Tyr-7, Phe-52 to Cys-61, Val-118 to Ser-125.
768055	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 934 as residues: Asp-39 to Ser-46, Lys-92 to Lys-99, Val-165 to Phe-172, Lys-252 to Ala-261, Asn-268 to Ala-273.
769685	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 935 as residues: Pro-129 to Arg-135.
771920	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 936 as residues: Pro-47 to Val-53, Asp-85 to Phe-97, Val-136 to Gly-144, Pro-166 to Glu-172, Leu-190 to Ser-197.
772790	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 937 as residues: Leu-5 to Trp-13, Met-20 to Leu-39, Ile-50 to Pro-63, Glu-66 to Ser-72, Leu-112 to Gln-120, Ala-141 to Lys-146, Tyr-165 to Asp-173.
772916	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 938 as residues: Lys-16 to Arg-25.
773632	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 940 as residues: Arg-1 to His-33.
774364	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 941 as residues: Ser-97 to Asn-103.
775355	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 942 as residues: Ser-40 to Ala-46.
775844	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 943 as residues: Leu-20 to Ser-31, Thr-38 to Val-47.
777760	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 944 as residues: Thr-22 to Ser-28, Thr-35 to Glu-42, Met-47 to Thr-55.
779837	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 945 as residues: Thr-26 to Arg-31, Leu-75 to Lys-100.
780769	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 946 as residues: Gly-1 to Asp-7, Lys-25 to Lys-31, Tyr-65 to Gly-70, Thr-100 to Arg-106, Pro-118 to Glu-124, Lys-162 to Ser-172, Leu-176 to Leu-182.
781445	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 947 as residues: Asn-33 to Lys-38, Leu-67 to Met-73, Ser-111 to Lys-121, Lys-127 to Leu-134, Pro-153 to Trp-158, Lys-237 to Met-249, Pro-280 to Tyr-292.
781531	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 948 as residues: Ala-8 to Pro-23, Gln-56 to Cys-61, Asn-66 to Pro-72.
783018	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 949 as residues: Asn-4 to Leu-17, Gly-19 to Phe-26, Pro-37 to Glu-43, Val-58 to Ser-64, Gln-80 to Gly-85.
783097	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 950 as residues: Pro-1 to Asp-9, Pro-24 to Gly-40, Pro-47 to Thr-55, Gln-62 to Ser-76.
784198	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 951 as residues: Met-1 to Arg-15, Leu-43 to Glu-48, Asp-55 to Asp-62, Ser-111 to Lys-160.
784868	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 952 as residues: Trp-8 to Gly-17, Glu-20 to Arg-35, Gly-40 to Cys-45, Ser-59 to Ser-64, Ala-73 to Leu-78, Val-85 to Leu-91, Arg-130 to Lys-135, Leu-138 to Glu-146, Pro-188 to

	Pro-194, Ser-206 to Cys-212, Ser-232 to Ala-246, Asp-293 to Ser-298.
785428	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 953 as residues: Arg-9 to Met-20, Glu-28 to Gly-33, Asn-49 to Lys-57, Thr-67 to Arg-75, Ser-81 to Leu-87, Glu-103 to Thr-109, Pro-115 to Ile-120, Asn-146 to Ser-174, Ser-177 to His-195, Met-197 to Ile-221, Asp-232 to Glu-240, Glu-289 to Phe-302, Cys-306 to Arg-314, Ser-357 to Ser-366, Lys-385 to Glu-401, Val-419 to Asp-427.
785845	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 954 as residues: Arg-41 to Asp-52, Pro-82 to Arg-94, Pro-102 to Gln-107, Gln-170 to Tyr-181, Glu-248 to Lys-254, Asp-277 to Gly-287, Ala-302 to Arg-308, Thr-367 to Gly-374.
785854	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 955 as residues: Asp-1 to Asp-17, Cys-59 to Asp-65.
787279	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 958 as residues: Lys-13 to Lys-20.
789002	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 959 as residues: Met-20 to Glu-29.
789008	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 960 as residues: Ser-24 to Arg-33, Ile-44 to Gly-57, Arg-63 to Asn-72, Ile-76 to Pro-82.
789555	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 961 as residues: Trp-106 to Thr-117, Trp-156 to Gln-163, Gln-173 to Asp-178, Gln-227 to Glu-233, Gln-255 to Glu-261, Glu-297 to Tyr-306, Thr-339 to Val-345, Leu-378 to Ile-385, Asp-414 to Lys-420, Cys-437 to Ile-444, Thr-491 to Gln-497, Glu-509 to Ser-515, Lys-526 to Glu-538.
789631	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 962 as residues: Thr-10 to Gly-18.
789779	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 963 as residues: Glu-1 to Ala-13, Leu-103 to Ser-109.
790387	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 964 as residues: His-1 to Ala-12.
790461	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 965 as residues: Glu-14 to Gly-23, Asp-47 to Met-53, Ala-55 to Thr-60, Pro-67 to Thr-73, Pro-78 to Gly-86, Tyr-91 to Pro-101, Ala-133 to Asn-139, Glu-169 to Gln-182, Glu-189 to Thr-195, Asn-197 to Arg-203, Gln-265 to Asp-271.
790931	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 966 as residues: Val-3 to Glu-13, Pro-29 to Pro-35, Glu-116 to Arg-125.
791176	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 967 as residues: Pro-1 to Pro-10, Pro-17 to Phe-28, Ser-61 to Pro-67.
792539	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 969 as residues: Ser-12 to Trp-17, Gln-20 to Lys-29, Asp-45 to Glu-51, Tyr-75 to Lys-83, Arg-103 to Gly-119, Gln-145 to Lys-155, Lys-166 to Leu-180, Thr-195 to Gly-203, Gln-209 to Val-219, Ser-222 to Ala-244, Leu-251 to Leu-260, Lys-277 to Lys-285.
792749	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 970 as residues: Ala-22 to Asp-41, Thr-61 to Met-66, Asp-191 to Lys-198, Arg-280 to Phe-287, Thr-289 to Lys-299, Pro-325 to Asp-332, Ser-351 to Arg-357.
793206	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 972 as residues: Gly-1 to Arg-6, Gln-11 to Arg-22, Glu-86 to Asp-91.
793626	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 974 as residues: Ser-1 to Gly-13, Gly-17 to Asn-26.
794417	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 975 as residues: Ser-7 to Trp-16.
795197	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 976 as residues: Ser-67 to Glu-73, Arg-129 to Gly-136, Phe-154 to Ala-161, Tyr-198 to Tyr-203, Pro-206 to Asp-212, Glu-222 to Cys-231.
795251	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 977 as residues: Phe-44 to Ser-50, Asp-57 to Pro-62, Asn-80 to His-90, Ser-110 to Ala-115, Ile-141 to Val-148, Glu-155 to Thr-173, Val-202 to Pro-217, Ile-221 to Val-229, Thr-

	233 to Ser-243, Val-253 to Thr-259, Ala-290 to Asn-320, Pro-322 to Ile-330, Ala-333 to Met-344, Val-362 to Leu-367, Asp-397 to Val-402, Glu-422 to Gly-448, Met-453 to Gly-460.
795752	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 978 as residues: Pro-52 to Asn-63, Pro-70 to Ile-79, Arg-93 to Gln-111.
796261	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 979 as residues: His-1 to Val-6, Cys-10 to Ser-15, Gly-26 to Ser-34, Trp-36 to Pro-58, Pro-96 to Thr-102, Pro-111 to Tyr-116, Phe-131 to Gly-138, Pro-184 to Leu-190, Glu-237 to Gly-244, Pro-255 to Lys-267, Lys-271 to Leu-280.
796933	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 980 as residues: Arg-1 to Pro-14, Gln-47 to Cys-52, Asn-57 to Pro-63, Ser-277 to Lys-282.
799424	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 981 as residues: Tyr-18 to Leu-27, Met-50 to Met-60, Leu-169 to His-178, Ser-233 to Ser-241.
799698	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 982 as residues: Pro-16 to Pro-21, Ala-54 to Glu-61, Ala-96 to Gly-105.
800351	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 983 as residues: Gly-21 to Gln-34, His-39 to Lys-53, Ser-63 to Tyr-71.
800573	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 984 as residues: Asp-33 to Arg-39, Ala-43 to Leu-48, Glu-256 to Gln-266, Gly-305 to Ile-311, Pro-314 to Ala-320, Gln-388 to Asn-394.
805815	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 985 as residues: Arg-1 to Lys-22, Ser-34 to Arg-48, Thr-64 to Arg-70, Pro-81 to Phe-89, Arg-148 to Asn-154, Tyr-172 to Asp-185, Ser-205 to Asp-216, Tyr-278 to His-285, His-294 to Pro-299, Glu-326 to Gly-333, Gly-336 to Ser-345.
806445	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 986 as residues: Arg-15 to Gly-24, Lys-26 to Trp-32.
810309	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 987 as residues: Pro-33 to Phe-50, Ile-57 to Gly-62, Gln-72 to Asn-85, Ala-87 to Thr-172.
811022	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 988 as residues: Ala-1 to Met-11, Gln-62 to Trp-68, Ala-89 to Val-99.
811023	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 989 as residues: Tyr-54 to Lys-61, Met-64 to Thr-70.
811143	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 990 as residues: Ala-1 to Ser-7, Ser-19 to Gly-36, Arg-53 to Pro-58, Thr-87 to Glu-102, Arg-115 to Tyr-120, Thr-159 to Thr-164, Ala-171 to Ser-179, Ala-206 to Pro-217, Pro-224 to Ala-233, Arg-253 to Ser-259.
813000	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 993 as residues: Tyr-25 to Lys-30, Lys-36 to Ile-43, Lys-52 to Gln-69, Glu-76 to Asp-81, Arg-92 to Trp-104, Leu-120 to Lys-126, Ser-129 to Ser-135, Ser-139 to Thr-156, Pro-165 to Glu-178, Ser-181 to Thr-186, Tyr-196 to Lys-201, Cys-225 to Lys-230, Glu-234 to Ser-242.
813431	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 995 as residues: Leu-23 to His-29, Pro-38 to Leu-46, Ser-59 to Gly-68, Pro-85 to Lys-108, Arg-119 to Phe-124, Ser-139 to Lys-156.
813450	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 996 as residues: Asn-1 to Trp-10.
813478	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 997 as residues: Ala-8 to Arg-14, Ile-64 to Thr-69, Val-94 to Asp-101, His-112 to Gln-117, Tyr-139 to Glu-145, Tyr-195 to Cys-208, Gly-216 to Gly-223, Asp-297 to Ser-307, Gly-378 to Leu-383, Ile-391 to Pro-404, Asn-451 to Ser-466.
813505	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 998 as residues: Thr-1 to Ala-20, Pro-22 to Lys-27, His-44 to Thr-51, Pro-53 to Thr-60, Arg-62 to Lys-79, Lys-97 to Asn-103, Pro-139 to Lys-144.
815552	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 999 as residues: Pro-1 to Ser-6, Pro-25 to Cys-31, Arg-142 to Lys-150.

815606	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1000 as residues: Arg-1 to Ala-11.
816048	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1001 as residues: Ala-13 to Thr-24, Glu-30 to Gln-39, Arg-69 to Gly-77, Gln-119 to Gly-126, Tyr-156 to Asn-162, Ser-184 to Gly-191.
823981	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1004 as residues: Lys-1 to Cys-7, Ala-11 to Lys-17, Glu-90 to Ile-95, Asn-141 to Arg-148, Leu-158 to Ala-163, Ala-171 to Thr-177.
824364	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1005 as residues: Gln-43 to Gly-54.
824423	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1006 as residues: Cys-33 to Arg-42, Val-53 to Met-63, Lys-71 to Lys-78, Gly-107 to Pro-118, Ala-159 to Leu-165, Val-272 to Arg-284, Pro-422 to Pro-427, Arg-437 to Gln-443, Ala-474 to Asp-482, His-519 to Cys-525, Ala-529 to Gln-535, Arg-540 to Gln-548.
825279	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1007 as residues: Ser-8 to Arg-14, Asp-23 to Gly-28, Ser-30 to Pro-37, His-52 to Ala-57, Pro-65 to Ser-74, Pro-112 to Ser-118, Ala-181 to Pro-189.
825548	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1009 as residues: Pro-2 to Ser-9.
825725	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1010 as residues: Pro-1 to Gly-8, Leu-95 to Lys-100, Glu-118 to Thr-125, Ser-162 to Lys-167, Arg-201 to Tyr-206.
827079	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1012 as residues: Arg-9 to Ser-17.
827153	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1013 as residues: Val-32 to Ala-44, Pro-49 to Ser-57, Gln-77 to Gly-82, Asp-116 to Gly-127, Arg-165 to Asn-172.
827351	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1014 as residues: Gly-5 to Lys-11, Ser-59 to Lys-67, Glu-130 to Arg-136, Asn-176 to Leu-183.
827503	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1015 as residues: Asp-61 to Val-67, Arg-113 to Asp-119, Ser-180 to Gly-191, Pro-199 to Ser-211, Ser-228 to Asn-238, Gly-276 to Ser-286, His-343 to Gly-351, Gln-354 to Arg-366, Leu-368 to Gln-382, Pro-393 to Ser-400, Asp-412 to Cys-418, Gly-430 to Leu-435, Gln-445 to Asp-450, Lys-484 to Val-491, Leu-513 to Gly-520.
827563	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1016 as residues: Pro-69 to Ala-81, Pro-84 to Gly-91, Ala-106 to Leu-112, Arg-216 to Lys-224, Trp-239 to Gly-250.
827565	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1017 as residues: Ala-1 to Ser-8, Ser-88 to Gly-96, Asn-121 to Asp-128, Cys-191 to Gly-196, Met-242 to Thr-248.
827893	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1018 as residues: Ser-41 to Ala-50, Glu-72 to His-77, Ala-120 to Glu-125, Thr-144 to Ile-153.
828072	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1019 as residues: Lys-30 to Leu-35.
828241	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1021 as residues: Gly-35 to Phe-45, Pro-47 to Arg-55, Glu-62 to Leu-70, Arg-102 to Tyr-111, Phe-128 to Gln-134, Val-139 to Met-144, Ser-180 to Gly-188, Lys-214 to Leu-219, Ser-241 to Glu-246, Phe-292 to Thr-298.
828287	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1022 as residues: Ala-12 to Thr-21, Ala-23 to Gly-31, Leu-43 to Gly-51, Lys-127 to Val-134.
828371	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1024 as residues: Gln-1 to Ala-6, Lys-50 to Pro-71, Pro-98 to Ser-111, Asp-148 to His-164, Asp-185 to Arg-191, Asp-238 to Gly-244, Pro-262 to Cys-274.
828403	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1025 as residues: Gly-1 to Trp-15, Arg-73 to Leu-82.
828501	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1026 as

	residues: Arg-99 to Arg-105, Pro-171 to Ser-176, Lys-189 to Val-195, Lys-291 to Ala-296.
828527	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1028 as residues: Glu-58 to Cys-63.
828538	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1029 as residues: Pro-9 to Thr-24, Thr-46 to Gly-52, Ser-70 to Thr-76, Ser-142 to Thr-149, Pro-154 to Ser-171, Glu-189 to Ser-196.
828541	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1030 as residues: Arg-9 to Pro-23, Gln-64 to Leu-69, Asp-76 to Asn-83, Lys-88 to Gln-93, Pro-129 to Thr-135, Gly-194 to Gly-203, Asp-223 to Gly-231, Thr-265 to Ile-281, Leu-287 to Lys-297.
828549	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1031 as residues: Pro-22 to Asn-28.
828562	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1032 as residues: Arg-26 to Asp-33, Asp-42 to Pro-58, Thr-63 to Lys-70, Thr-103 to Asp-114.
828576	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1033 as residues: Arg-11 to Gly-17, Pro-26 to Gly-31, Ala-48 to His-58.
828602	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1034 as residues: Tyr-1 to Met-8, Leu-10 to Lys-26, Pro-47 to Pro-54, Lys-128 to Ser-133.
828628	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1035 as residues: Thr-124 to Thr-129, Gly-136 to Phe-142, Asp-164 to His-171, Asp-180 to Tyr-194.
828684	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1037 as residues: Ser-16 to Thr-22, Arg-39 to Ala-51, Arg-60 to Gly-65, Thr-67 to Arg-90, Lys-109 to Gln-125, Ser-146 to Arg-159, Gln-166 to Thr-176, Glu-192 to Tyr-197, Val-267 to His-279, Ala-351 to Gly-356, Phe-363 to Gly-368, Gly-387 to Arg-392, Asp-488 to Ala-498.
828727	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1038 as residues: Gly-14 to Val-21, Asp-40 to Gln-57, Gln-86 to Tyr-93, Gln-98 to Asp-104, Lys-124 to Asp-130, Gln-138 to Cys-156, Tyr-170 to Gln-175, Gln-196 to Ala-201.
828734	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1039 as residues: Asp-5 to Trp-19, Ile-37 to Pro-42, Asp-52 to Asp-72, Glu-85 to Ser-92, Ser-107 to Leu-117, Asp-128 to His-147.
828842	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1041 as residues: Ala-25 to Phe-32, Glu-54 to Ser-61, Thr-74 to Glu-79, Glu-99 to Lys-105, Glu-112 to Glu-121.
828843	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1042 as residues: Pro-3 to Asn-11, Gln-46 to Ala-51, Asn-62 to Lys-74, Val-108 to Gln-113, Arg-119 to Gly-163, Ala-223 to Lys-237.
828851	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1043 as residues: Thr-3 to Lys-8, Leu-63 to Val-70, Lys-141 to Val-149, Ile-326 to Thr-333.
828856	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1044 as residues: Leu-1 to Gly-10.
828862	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1045 as residues: Pro-1 to Pro-9, Arg-81 to Glu-87, Gln-114 to Glu-119.
828870	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1046 as residues: Ser-1 to Gly-18, Trp-25 to Gly-31, Arg-46 to Ser-52, Ala-103 to Ala-108, Ser-154 to Gly-165, Gln-228 to Pro-236, Ser-284 to Gly-291, Ala-321 to Asp-327, Lys-377 to Asn-394, Asp-406 to Ser-416.
828873	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1047 as residues: Tyr-15 to Gly-20, Asn-72 to Asp-80, Pro-105 to Pro-110, Gln-149 to Arg-154, Glu-161 to Gly-167, Ile-312 to Asp-318, Lys-353 to Leu-361, Arg-379 to Thr-385, Pro-423 to Trp-435, Pro-437 to Cys-444, Asn-450 to Met-466.
828892	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1048 as residues: Asp-19 to Asn-25, Gly-67 to Glu-79.
828893	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1049 as

	residues: Ser-55 to Thr-60, Glu-97 to Ser-103, Thr-164 to Glu-170, Gly-192 to Gly-197, Leu-204 to Ser-218, Ala-238 to Ser-250, Asp-265 to Tyr-292, Gly-298 to Gly-307, Gly-351 to Met-359, Phe-389 to Glu-400.
828897	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1050 as residues: Phe-28 to Arg-33.
828910	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1051 as residues: His-1 to Ile-13, Arg-20 to Glu-64, Arg-83 to Gln-89, Tyr-145 to Asp-152.
828927	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1052 as residues: Glu-10 to Pro-21, Thr-54 to Gly-60, Cys-79 to Glu-90, Lys-154 to Lys-159.
828932	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1053 as residues: Arg-1 to Arg-9, Phe-54 to Pro-60, Gln-74 to Gly-90, Asn-114 to Gly-119, Cys-124 to Ser-132, Thr-139 to Leu-151, Asp-171 to Lys-182, Ala-188 to Leu-193, Val-203 to Trp-222, Lys-230 to Glu-236, Glu-244 to Asp-250, Leu-258 to Gly-268, Gly-283 to Asp-288, Ser-291 to Trp-297, Gly-300 to Ala-308.
828933	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1054 as residues: Glu-21 to Ser-34, Thr-130 to Tyr-138.
828941	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1055 as residues: Gly-1 to Ala-6, Pro-15 to Gly-22, Asn-160 to Gln-177, Asn-193 to Asp-199, Glu-205 to Leu-211.
828963	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1057 as residues: Pro-48 to Gly-54, Ser-56 to Ser-76, Lys-102 to Pro-107, Ser-146 to Gly-153, Ser-208 to Arg-213, Tyr-285 to Leu-299, Pro-314 to Phe-319, Asn-322 to Asn-327.
828964	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1058 as residues: Thr-36 to Cys-47.
828966	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1059 as residues: Gly-1 to Ser-16, Met-26 to Pro-31, Lys-128 to Glu-134, His-165 to Gln-170, Asp-207 to Asn-216, Pro-348 to Arg-359, Lys-433 to Ala-439, Gly-448 to Tyr-457.
828967	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1060 as residues: Met-135 to Arg-141, Gly-149 to Lys-166, Ile-188 to Ser-196, Gly-203 to Tyr-213, Gln-267 to Asp-278, Arg-298 to Trp-317, Leu-319 to Leu-326, Gln-344 to Thr-349, Pro-410 to Ser-419, Ala-500 to Ala-510.
828977	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1061 as residues: Gly-32 to Tyr-42, Asn-52 to Glu-58, Ser-78 to Gly-87, Lys-97 to Gly-109, Glu-116 to Arg-127, Pro-147 to Pro-152, Pro-162 to Asn-171, Leu-179 to Glu-185, Ile-203 to Glu-208, Val-222 to Gln-228.
828978	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1062 as residues: Asp-24 to Lys-30, Arg-49 to Lys-62, Arg-121 to Thr-149, Gly-163 to Leu-171, Ala-186 to Glu-195, Glu-216 to Ser-221, Ile-229 to Ser-236, Lys-258 to Lys-264, Lys-305 to Arg-313.
829001	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1064 as residues: Thr-11 to Cys-24, Arg-48 to His-55, Arg-62 to Gly-70.
829003	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1065 as residues: Lys-14 to Gly-22, Ser-61 to Asp-66, Cys-80 to Lys-91, Lys-97 to Arg-107, Gly-135 to Asn-146, Lys-198 to Lys-208, Met-221 to Thr-227, Phe-244 to Gly-256, Asp-292 to Gln-300.
829016	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1066 as residues: Arg-1 to Asp-11, Ala-17 to Gln-25, Glu-30 to His-37, Cys-39 to Thr-44, Asn-86 to Phe-93.
829027	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1067 as residues: Pro-1 to Ser-7, Thr-45 to Leu-63, Arg-113 to Thr-118, Pro-172 to Gly-182.
829028	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1068 as residues: Ser-1 to Gln-19, Gly-32 to Phe-39, Ala-95 to Arg-116, Lys-122 to Glu-142, Ile-148 to Asn-156, Ser-168 to Asn-191, Ala-196 to Thr-204, Ser-289 to Lys-304, Leu-308 to Ser-314, Thr-332 to Ile-341.
829034	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1070 as residues: Ser-32 to Ala-43, Thr-62 to Glu-69, Phe-128 to Thr-156, Thr-179 to His-188,



	Gly-196 to Glu-203, Pro-205 to Ala-219, Gln-221 to Ile-230, Pro-246 to Thr-255, Thr-271 to His-276, Asn-324 to Thr-344, Pro-364 to Ala-370, Tyr-427 to Arg-434, Gly-440 to Pro-445.
829036	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1071 as residues: Leu-16 to Phe-21, Thr-69 to Lys-74, Asn-87 to His-92, Thr-126 to Leu-137, Phe-154 to Lys-164, Ala-171 to Asp-178, Ile-192 to Thr-203, Glu-261 to Ser-273.
829049	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1072 as residues: Gly-50 to Tyr-59.
829073	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1073 as residues: Asn-1 to Met-6, Asn-26 to Ser-35, Pro-43 to Ile-54.
829075	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1074 as residues: Gly-14 to Pro-30, Ser-64 to Ser-69, Asn-97 to Arg-109.
829076	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1075 as residues: Lys-84 to Gly-94, Asn-142 to Ile-147.
829080	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1076 as residues: Gly-13 to Trp-23, Pro-39 to Gly-44.
829087	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1077 as residues: Pro-13 to Arg-24.
829095	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1079 as residues: Pro-8 to Pro-13.
829118	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1081 as residues: Arg-7 to Val-12, Ile-52 to Thr-70, Ser-86 to Asp-91, Thr-126 to Ser-138.
829152	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1082 as residues: Asp-12 to Ser-19.
829160	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1083 as residues: Ala-7 to Arg-20.
829163	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1084 as residues: Ser-23 to Asp-32, Val-36 to Glu-59, Ser-65 to Asn-76, Cys-91 to Ser-102, Pro-108 to Leu-115, Thr-151 to Gln-164, Glu-167 to Lys-176.
829176	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1085 as residues: His-1 to Asn-8, Cys-22 to Arg-27, Gly-34 to Ser-44, Tyr-60 to Ser-65, Ser-118 to Gln-123, Ser-149 to Trp-154, Pro-159 to Gly-168, Gln-207 to Leu-220.
829204	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1086 as residues: Ala-11 to Ser-19, Thr-104 to Lys-133.
829207	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1087 as residues: Lys-5 to Ser-11, Pro-31 to Ser-37, Pro-87 to Asp-92, Asp-115 to Lys-123, Ser-149 to Arg-155, Thr-243 to Pro-253.
829228	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1088 as residues: Pro-1 to Trp-6, Leu-73 to Tyr-79, Glu-108 to Thr-117, Asp-136 to Asp-142, Ser-201 to Pro-207, Leu-224 to Pro-233, Val-242 to Ala-248, Ser-312 to Leu-319, Val-349 to Ser-359, Ala-362 to His-368, Thr-370 to Gly-376, Lys-403 to Tyr-409, Glu-426 to Arg-431, Lys-455 to Asp-460, Arg-499 to Thr-505, Asp-561 to Ser-570, Ser-665 to Ser-673.
829252	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1089 as residues: Thr-9 to Val-16.
829269	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1091 as residues: Ser-1 to Glu-7, Lys-76 to Gln-83.
829277	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1092 as residues: Lys-88 to Phe-97, Thr-106 to Leu-120, Thr-147 to Pro-152, Pro-173 to Met-179.
829290	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1093 as residues: Pro-1 to Pro-19, Pro-25 to Lys-30.
829308	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1096 as residues: Met-26 to Asn-37, Glu-42 to Gln-51, Thr-68 to Ser-95, Ala-97 to Lys-113, Asp-156 to Val-161, Val-208 to Asp-215, Pro-217 to Ala-228.
829349	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1097 as

	residues: Asn-18 to Lys-24, Asp-87 to Asn-94, Glu-116 to Gly-125.
829354	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1098 as residues: Ala-1 to Asn-16, Pro-36 to Arg-43.
829388	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1099 as residues: Glu-91 to Pro-100, Tyr-122 to Thr-127, Thr-168 to Val-173, Thr-210 to Asp-215, Leu-219 to Gly-224, Gly-232 to Val-237.
829626	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1101 as residues: Gly-145 to Ala-151.
829730	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1102 as residues: Pro-22 to His-27, Pro-87 to Asp-93, Arg-109 to Lys-115, Arg-172 to Glu-177, Glu-219 to Asp-226.
829892	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1103 as residues: Tyr-36 to Ala-46, Val-58 to Asn-63, Glu-73 to Asn-78, Asn-90 to Asn-95, Ser-125 to Leu-133, Glu-143 to Pro-150, Phe-186 to Leu-191, Leu-274 to Glu-281, Lys-303 to Phe-308, Thr-323 to Gly-330.
829938	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1105 as residues: Thr-1 to Pro-14, Ser-36 to Thr-57, Ser-81 to Thr-91, Glu-103 to Leu-110, Glu-124 to Tyr-130, Ala-135 to Lys-140, Leu-146 to Glu-162, Lys-167 to Glu-172, Glu-199 to Val-213.
829969	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1106 as residues: Arg-12 to His-21, Arg-77 to Ser-88.
829982	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1107 as residues: Arg-6 to His-14, Ser-40 to Met-47, Thr-68 to Cys-74, Ile-97 to His-115, Gly-118 to Pro-124.
830007	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1108 as residues: Ala-7 to Ala-16.
830019	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1109 as residues: Leu-21 to Pro-27.
830073	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1110 as residues: Gly-16 to Val-22, Pro-45 to Lys-50, Phe-58 to Arg-65, Ser-135 to Gly-141, Gly-153 to Ser-158, Pro-160 to Tyr-168.
830148	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1114 as residues: Asp-63 to Lys-81, Gly-101 to Gly-108, Pro-182 to Ala-200, Pro-210 to Met-216, Pro-235 to Gly-243.
830183	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1117 as residues: Pro-29 to Lys-37, Pro-40 to Val-47, Tyr-62 to His-67.
830194	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1118 as residues: Ala-43 to Lys-51, Glu-66 to Leu-74, His-81 to Glu-88, Arg-98 to Ser-105, Gly-111 to Gln-116, Leu-166 to Lys-182, Leu-261 to Ala-273, Glu-294 to Arg-302, Glu-335 to Asp-347.
830207	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1119 as residues: Pro-14 to Pro-48, Asp-55 to Gly-61, Lys-94 to Asn-99, Ala-107 to Ser-115, Ile-117 to Asn-124, Thr-133 to Cys-139, Thr-142 to Ile-147, Gly-163 to Ser-169.
830242	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1120 as residues: Glu-29 to Lys-34, Leu-151 to Gln-157, Arg-160 to Ser-171, Gln-177 to Pro-190.
830328	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1121 as residues: Pro-18 to Met-24, Glu-66 to Gln-78, Ala-85 to Arg-93, Glu-99 to His-108, Leu-114 to Asp-137, Pro-171 to Gln-176, Gly-205 to Leu-213.
830340	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1122 as residues: Gly-12 to Lys-18, Arg-46 to Glu-56, Leu-67 to Gly-73, Ala-91 to Tyr-112.
830341	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1123 as residues: Leu-14 to Gln-20, Asn-34 to Glu-41, Lys-193 to Asn-198.
830351	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1124 as residues: Pro-1 to Leu-13, Gly-42 to Pro-51, Arg-64 to Ala-69, Met-104 to Asp-109, Cys-125 to Trp-132, Asp-161 to Trp-175, Glu-206 to Glu-218.

830358	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1125 as residues: Cys-75 to Thr-81.
830400	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1127 as residues: Pro-1 to Gly-6, Arg-17 to Arg-33, Glu-151 to Trp-157, Ile-187 to Tyr-193, Lys-249 to Glu-258, Asn-289 to Ser-294, Pro-340 to Lys-353.
830437	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1128 as residues: Ala-87 to Ser-94, Asp-104 to Arg-112, Leu-114 to Asp-119, Ser-186 to Thr-202.
830466	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1130 as residues: Pro-14 to Ile-24, Thr-35 to Phe-42, Ser-45 to Asn-57, Pro-65 to Trp-89.
830497	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1131 as residues: Thr-1 to Leu-9, Ser-46 to Leu-56, Glu-117 to Lys-124, Pro-129 to Asp-135, Ala-144 to Gln-150, Gly-156 to Lys-162, Phe-182 to Pro-187, Pro-196 to Gln-201, Lys-217 to Asp-227.
830511	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1132 as residues: Lys-13 to Cys-44, Lys-101 to Arg-109, Gln-120 to Gly-129.
830540	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1135 as residues: Leu-31 to Lys-37, Arg-48 to Asn-54.
830550	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1136 as residues: Pro-8 to Cys-15, Val-80 to Cys-85.
830567	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1137 as residues: Lys-28 to Leu-33, Pro-60 to Ser-66.
830586	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1138 as residues: Pro-1 to Gln-15, Arg-33 to Leu-40, Arg-72 to Ser-78, Leu-98 to Asp-103, Phe-116 to Gly-124, Pro-152 to Arg-158, Thr-193 to Pro-200, Leu-213 to Phe-219, Asp-229 to Lys-237, Lys-246 to Lys-258, Arg-275 to Thr-280, Thr-306 to Lys-312, Leu-320 to Arg-328, Ala-335 to Asn-340, Gly-342 to Trp-349, Cys-364 to Pro-372.
830632	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1139 as residues: Ala-6 to Thr-14, Arg-143 to Lys-148.
830659	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1142 as residues: Thr-32 to Tyr-40, Ala-67 to Gln-82, Arg-128 to Thr-133, Leu-137 to Thr-146, Pro-187 to Ser-193.
830696	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1143 as residues: Glu-83 to Lys-91.
830743	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1145 as residues: Pro-11 to Phe-16, Thr-48 to Ser-60.
830770	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1146 as residues: Thr-36 to Thr-44.
830830	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1147 as residues: Lys-73 to Thr-78, Pro-84 to Pro-96, Lys-107 to Glu-124, Ile-142 to Cys-153, Asp-179 to Asn-184.
830838	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1148 as residues: Ser-17 to Arg-22, Gly-48 to Val-56, Asn-217 to Asp-223, Thr-238 to Asn-243.
830851	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1149 as residues: Arg-1 to Val-7, Ala-156 to Phe-162, Arg-216 to Lys-239.
830856	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1151 as residues: Trp-29 to Gly-35, Thr-41 to His-47, Val-95 to Lys-111.
830862	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1152 as residues: Arg-14 to Val-22, Ala-24 to Gly-35, Arg-37 to Lys-58, Ala-88 to Ala-94, Lys-164 to Ser-172.
830879	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1153 as residues: Cys-34 to Leu-44, Ser-60 to Gly-69, Asp-118 to Gly-123, Cys-148 to Gln-154.
830919	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1154 as residues: Pro-1 to Ser-41, Arg-53 to Pro-61, Arg-66 to Gln-132.

830969	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1155 as residues: His-17 to Pro-27, Phe-31 to Val-38, Gly-53 to Thr-62.
830991	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1156 as residues: Arg-1 to Pro-14, Ala-44 to Ser-56, His-69 to Lys-75, Gly-89 to Lys-98, Tyr-101 to Tyr-121, Pro-123 to Thr-131, Pro-149 to Gly-171, Tyr-186 to Glu-192.
831002	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1157 as residues: Glu-63 to Asn-73, Pro-114 to Tyr-122, Ser-194 to Glu-201, Ile-263 to Ser-269.
831003	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1158 as residues: Ile-9 to Leu-17, Asp-63 to Gly-70, Leu-112 to Ala-128.
831021	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1159 as residues: Asn-6 to Asp-12.
831036	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1160 as residues: Ser-6 to Ser-25, Tyr-37 to Lys-42, Arg-49 to Tyr-54, Pro-56 to Glu-61, Gln-72 to Cys-77, Lys-104 to Glu-110, Lys-134 to Met-142, Asp-147 to Arg-158, Arg-189 to Asn-194.
831071	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1161 as residues: Thr-41 to Arg-49, Glu-137 to Asp-142, Tyr-158 to Glu-163, Arg-184 to Thr-199, Arg-239 to Gly-253, Pro-297 to Gly-304, Pro-319 to Ile-327, Leu-347 to Val-356, Asn-435 to Leu-441, Asp-443 to Ser-452, Ala-457 to Thr-462, Asp-479 to Arg-484, Gly-510 to His-516, Glu-555 to Thr-565, Asp-597 to Ser-602, Thr-615 to Asp-622, Val-653 to Leu-661, Ala-684 to Arg-697, Ser-704 to Glu-712, Ala-731 to Ala-737, Lys-800 to Met-805.
831099	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1163 as residues: Leu-12 to Gly-18, Leu-93 to Ile-98, Lys-165 to Ser-183, Thr-198 to Lys-211, Glu-232 to Gly-237, Pro-239 to Gly-249, Arg-257 to Asp-278, Cys-292 to Glu-297, Arg-306 to Ser-316, Asp-323 to Asn-331, Glu-347 to Gly-354, Thr-365 to Asn-370, Pro-390 to Thr-396, Asn-420 to Ser-433, Val-440 to Gln-451, His-457 to Asp-465, Phe-533 to Met-538, Ala-540 to Tyr-550, Pro-560 to Lys-565.
831113	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1164 as residues: Ser-26 to Arg-33, Pro-51 to Thr-56, Cys-82 to Asp-94, Pro-104 to Gly-128.
831120	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1165 as residues: Ala-39 to Leu-47, Val-49 to Lys-55, Thr-66 to Asp-75, Thr-85 to Gly-104, Ala-114 to Gly-147, Pro-176 to Thr-199, Ser-205 to Ser-221, Glu-233 to Lys-240, Lys-246 to Asp-251, Glu-256 to Ser-267, Ser-291 to Leu-302, Thr-305 to Asp-324, Cys-336 to Val-345, Phe-367 to Cys-375.
831172	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1166 as residues: Pro-1 to Gly-7, His-119 to Gly-125, His-145 to Asp-151, Leu-173 to Leu-178.
831178	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1167 as residues: Glu-37 to Asn-42, Ser-48 to Thr-54, Pro-101 to Glu-106.
831184	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1168 as residues: Gln-1 to Pro-29.
831203	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1169 as residues: Thr-1 to Ser-6, Leu-10 to Asn-23, Gln-31 to Arg-36, Arg-43 to His-49, Ala-58 to Leu-63, Gln-81 to Asp-105, Glu-113 to Ile-122, Pro-132 to Lys-137, Ser-175 to Gln-181.
831257	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1173 as residues: Arg-87 to Leu-96, His-104 to Lys-112, Asp-144 to Pro-150.
831277	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1174 as residues: Arg-1 to Gly-13.
831317	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1175 as residues: Ser-97 to Lys-102, Thr-108 to Gly-119, Lys-151 to Gly-157, Pro-204 to Glu-210, Gln-224 to Gly-230, Val-238 to Cys-245, Met-279 to Asn-284, Gly-332 to Glu-349.
831339	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1176 as

	residues: Met-1 to His-19, Pro-21 to Pro-27, Ala-49 to Glv-59, Pro-82 to Ala-104.
831363	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1177 as residues: Thr-1 to Ser-14, Thr-82 to Pro-89, Met-102 to Ala-109, Phe-117 to Ile-124, Asp-142 to Arg-148, Thr-196 to Trp-205, Gln-304 to Leu-310, Gln-325 to Ser-331, Gly-387 to Thr-393, Ala-415 to Lys-430, Pro-469 to Pro-477, Gly-500 to Ile-506, Arg-521 to Glv-529, Pro-534 to Glv-541, Gln-553 to Lys-558, Ala-571 to Glu-579.
831385	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1180 as residues: Ser-1 to Thr-9, Ala-32 to Asn-37, Thr-40 to Tyr-49, Gln-71 to Thr-80.
831390	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1181 as residues: Trp-50 to Gly-55, Leu-109 to Val-119, Phe-146 to Asp-158, Ser-165 to Trp-172, Phe-192 to Ile-197, Leu-241 to Asp-252, Lys-268 to Pro-273, Ser-310 to Lys-315, Asp-334 to Ala-342, Pro-348 to Tyr-353.
831391	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1182 as residues: Ser-28 to Pro-38, Pro-45 to Cys-55, Leu-70 to Ser-77, Glu-98 to Phe-104, Asp-112 to Ser-122, Thr-152 to Lys-158.
831405	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1183 as residues: Asp-47 to Ser-55, Glu-86 to Cys-95, Glu-105 to Gly-113, Gln-133 to Asn-138, Arg-144 to Asp-156.
831476	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1185 as residues: Gln-28 to Gly-33, Asp-41 to Trp-47, Asn-51 to Ser-56, Ser-73 to Asn-83, Trp-111 to Asn-117, Leu-133 to Gln-138, Arg-143 to Tyr-150, Thr-156 to Glu-165.
831488	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1186 as residues: Glu-53 to Asn-59, Lys-97 to Phe-104, Lys-133 to Ala-138.
831519	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1188 as residues: Ser-17 to Gly-25, Thr-47 to Leu-59, His-71 to Arg-77, Pro-83 to Gln-90, Tyr-133 to Ser-143, Arg-160 to Gly-169, Pro-188 to Val-193, Glu-202 to Glu-208, Leu-283 to Arg-288, Glu-295 to Leu-301, Ala-327 to Leu-333, Ala-426 to Pro-433, Leu-444 to Leu-456, Asn-492 to Ala-498.
831550	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1190 as residues: Arg-1 to Gly-15, Ser-42 to Trp-51, Pro-59 to Arg-64.
831560	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1191 as residues: Arg-58 to Asp-64.
831570	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1193 as residues: Thr-61 to Cys-74, Gly-92 to Cys-104, Cys-128 to Ser-133, Asn-179 to Gly-186, Ser-198 to Cys-226, Asn-265 to Ser-274, Ser-280 to Ile-285, Ser-291 to Asp-297, Leu-305 to Gly-315, Phe-317 to Gly-333, Asp-336 to Leu-344, Phe-354 to Cys-361.
831596	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1195 as residues: Gln-80 to Gly-85.
831627	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1196 as residues: Arg-1 to Ser-12, Gly-94 to Thr-106, Ser-161 to Leu-169, Ser-183 to Val-188, Glu-199 to Cys-205, Ser-246 to Ile-251, Leu-271 to Thr-276.
831649	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1197 as residues: Tyr-32 to Lys-39.
831664	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1198 as residues: Lys-1 to Asp-42, Arg-71 to Ala-76, Gln-138 to Phe-145, Lys-170 to Thr-178, Cys-186 to Asp-192.
831684	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1200 as residues: Ile-135 to Ala-140, Tyr-151 to Asn-157, Ser-183 to Ile-190, Gly-196 to Lys-201, Lys-226 to Lys-232, Asn-246 to Thr-252, Asp-293 to Gly-300.
831687	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1201 as residues: Ala-56 to Tyr-63.
831726	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1202 as residues: Arg-3 to Arg-15, Lys-34 to Thr-39, Asn-41 to Lys-59, Ala-104 to Glu-110.
831762	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1204 as residues: Pro-83 to Leu-91, His-116 to Ala-122, Pro-141 to Ser-155.
831848	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1206 as

	residues: Gln-16 to Thr-23.
831861	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1207 as residues: Ala-20 to Lys-26, Pro-59 to Pro-67, Ser-104 to Thr-121, Gln-130 to Gln-136.
831866	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1208 as residues: Arg-11 to Ala-24, Ile-39 to Lys-45, Arg-76 to Pro-85, Lys-124 to Lys-130, Pro-139 to Ser-153, Ala-156 to Glu-170, Ser-179 to Thr-184, Asp-234 to Gly-244, Gly-321 to Lys-329.
831899	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1210 as residues: Asp-11 to Trp-16, Pro-37 to Thr-44, Pro-74 to Pro-82, Arg-112 to Gln-119, Cys-126 to Arg-138, Arg-199 to Thr-204.
831913	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1211 as residues: Pro-22 to Cys-27, Glu-54 to Glu-60, Asp-112 to Phe-117, Lys-183 to Asp-189, Gln-277 to Tyr-282, Pro-325 to Arg-331, Gly-336 to Tyr-346.
831985	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1213 as residues: Cys-7 to Asp-12, Pro-21 to Gly-26.
831986	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1214 as residues: Cys-1 to Ser-7, Ala-62 to Gly-72, Pro-83 to Ala-101.
832010	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1215 as residues: Leu-1 to Lys-21, Glu-39 to Cys-47, Lys-49 to Gln-61, His-64 to Gly-76, Thr-83 to Lys-90, His-92 to Ile-99.
832016	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1216 as residues: Phe-28 to Asn-33, Leu-55 to Tyr-80, Pro-126 to Gly-132, Pro-162 to Gly-169, Pro-194 to Arg-201.
832041	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1217 as residues: Lys-55 to Met-63, Arg-120 to Asp-132, Gly-266 to Glu-281, Val-313 to Thr-319, Leu-361 to Ser-370, Tyr-406 to Met-412, Leu-465 to Trp-470.
832049	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1219 as residues: Leu-80 to Lys-87, Lys-102 to Thr-109, Glu-195 to Thr-200, Thr-203 to Asp-209.
832122	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1220 as residues: Asn-29 to Phe-36, Asp-41 to Ser-50.
832197	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1222 as residues: Glu-61 to Leu-70.
832237	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1223 as residues: Lys-28 to Val-35, Arg-41 to Arg-55, Pro-76 to Thr-87.
832246	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1224 as residues: Arg-17 to Asn-23, Arg-90 to Gly-95, Leu-114 to Glu-121, Pro-153 to Asp-158.
832256	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1225 as residues: Gly-15 to Asn-22.
832280	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1226 as residues: Glu-1 to Trp-16, Ala-32 to Glu-38, Ala-49 to Gln-55, Pro-61 to Gln-66, Ala-78 to Asp-100, Leu-107 to Thr-127, Pro-133 to Phe-157, Pro-160 to Thr-171, Leu-179 to Asp-196, Asp-201 to Lys-222, Pro-249 to Ile-254, Val-258 to Val-263, Thr-268 to Ser-277, Thr-279 to Ala-295, Gly-299 to Phe-327, Val-335 to Asp-346, Lys-366 to Asp-378.
832285	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1227 as residues: Phe-18 to Leu-23.
832294	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1228 as residues: Pro-21 to Gln-28, Pro-56 to Leu-64, Glu-79 to Pro-95, Met-125 to Gly-138.
832326	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1229 as residues: Ser-30 to Trp-45, Gln-64 to Cys-72, Pro-74 to Pro-80, Ala-92 to Arg-98, Trp-104 to Ser-112, Ser-129 to Asp-135, Pro-145 to Gln-152, Arg-168 to Gly-173, Gln-176 to Pro-183.
832370	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1232 as residues: Ala-5 to Ala-11, Pro-23 to Pro-36, Glu-72 to Gly-82, Pro-85 to Pro-91, Asp-

	98 to Gly-119, Pro-121 to Glu-127.
832381	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1233 as residues: Arg-1 to Glu-6, Arg-52 to Ala-58, Phe-72 to Leu-79, Gly-88 to Glu-93, Tyr-124 to Arg-134.
832454	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1235 as residues: Ala-23 to Asp-41.
832465	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1236 as residues: Ala-1 to Gly-7, Ala-32 to Val-45, Ile-65 to Ser-75, Ser-93 to Ser-108.
832475	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1237 as residues: Arg-1 to Val-10, Thr-65 to Ser-71, Arg-83 to Tyr-96, Trp-104 to Trp-111.
832495	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1238 as residues: Arg-9 to Arg-14.
832498	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1239 as residues: Pro-26 to Asp-31, Thr-113 to Gly-125, Asn-158 to Glu-163, Asn-288 to Val-293.
832501	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1240 as residues: Ser-8 to Glu-13.
832505	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1241 as residues: Ala-27 to Arg-46, Pro-54 to Arg-76, Arg-134 to Lys-140, Asn-148 to Ser-154, Lys-166 to Thr-172, Pro-175 to Gln-182, Asp-185 to Asp-192.
832554	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1243 as residues: Arg-26 to Val-31, Asn-122 to Thr-128.
832569	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1244 as residues: Gln-6 to Met-16.
832578	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1245 as residues: Arg-15 to Leu-27, Ser-62 to Gly-72, Pro-107 to His-112, Pro-122 to Gln-142, Glu-147 to Arg-158, Lys-177 to Lys-191, Leu-195 to Val-202, Leu-206 to Pro-218, Glu-228 to Gln-233, Asp-239 to Asp-244, Glu-258 to Gln-278.
832615	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1246 as residues: Gln-41 to Ala-48.
832632	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1248 as residues: Asn-60 to Val-70, Glu-93 to Trp-107, Arg-116 to Gln-125, Leu-133 to Lys-141, Lys-162 to Glu-167.
832633	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1249 as residues: Gly-8 to Trp-13, Pro-36 to Gly-41, Pro-91 to Ala-96.
834859	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1252 as residues: Tyr-16 to Leu-22, Asp-24 to Asp-34, Gly-43 to Ala-48, Gly-57 to Thr-68, Gly-118 to Ser-127, Ile-129 to Tyr-134, Pro-139 to Asp-162.
834861	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1253 as residues: Glu-14 to Glu-50, Glu-67 to Asp-74, Leu-89 to Asn-95.
834890	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1254 as residues: Arg-8 to Lys-13, Gly-35 to Lys-42, Ala-48 to Lys-54, Ala-105 to Leu-110, Gly-150 to Val-157, Phe-164 to Asn-173.
835079	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1255 as residues: Ser-53 to Pro-60.
835554	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1256 as residues: Ile-31 to Ile-38, Asp-116 to Arg-121, Phe-246 to Leu-251, Lys-280 to Tyr-291, Met-363 to Arg-373, Gly-381 to Trp-386.
835723	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1258 as residues: Glu-20 to Thr-26, Trp-47 to Ser-57, Pro-98 to Asn-105, Pro-124 to Phe-129, Ala-173 to Val-183, Lys-190 to Ser-196, Asn-277 to Asn-284, Glu-297 to Phe-306, Thr-322 to Lys-327, Gln-372 to Val-383, Pro-387 to Gly-395, Ser-406 to Thr-415, Arg-432 to Thr-442.
835791	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1259 as residues: Ala-4 to Gly-10.
835817	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1260 as

	residues: Glu-37 to Leu-43.
835840	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1261 as residues: Gln-1 to Asn-6, Pro-18 to Ile-31.
836048	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1262 as residues: Lys-1 to Lys-11, Tyr-27 to Glu-35, Glu-61 to Gly-68.
836898	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1263 as residues: Gln-94 to Lys-102, Gly-140 to Thr-154, Arg-173 to Asp-196, Thr-201 to Asp-206, Glu-241 to Gly-248.
836927	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1264 as residues: His-1 to Arg-12.
837344	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1265 as residues: Pro-15 to Ile-24.
837789	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1266 as residues: Ser-1 to Trp-7, Asp-47 to Ile-52, Pro-70 to Ser-80, Cys-89 to Thr-98, Ala-131 to Ser-142, Phe-169 to Cys-176, Gly-183 to Ser-193, Phe-202 to Pro-209, Arg-243 to Ala-249, Ser-256 to Lys-265, Arg-277 to Asp-284.
838754	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1268 as residues: Phe-27 to Ser-37, Tyr-91 to Arg-96, Pro-156 to Gln-164, Cys-207 to Val-216, Met-242 to Tyr-251.
839561	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1271 as residues: Arg-2 to Gly-7, Arg-16 to Gln-22, Phe-41 to Gly-49, Ala-60 to Asn-74, Leu-125 to Gln-131, Asp-170 to Pro-175, Ala-209 to Arg-218, Glu-222 to Glu-258, Ala-265 to Ser-300.
839816	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1272 as residues: His-32 to Arg-37, Ser-42 to Ser-48, Glu-77 to Glu-88.
840068	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1273 as residues: Ala-1 to Gln-14.
840279	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1274 as residues: Ala-1 to Asp-15.
840538	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1276 as residues: Ala-8 to Pro-13, Pro-18 to Gln-26, Lys-107 to Pro-114, Ala-149 to Arg-157, Ile-294 to Leu-299, Ser-356 to Pro-363, Pro-384 to Phe-392, Ala-474 to Gly-481, Ala-489 to Tyr-494, Pro-512 to Lys-517, Arg-623 to Thr-630, Lys-673 to Ser-678, Thr-703 to His-709, Arg-714 to Arg-720, Gly-755 to Glu-766.
840549	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1278 as residues: Ala-5 to Lys-15, Pro-28 to Gln-34, Tyr-105 to His-111, Gln-150 to Cys-157.
840557	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1280 as residues: Gly-34 to Leu-40, Thr-125 to Gly-134, Ala-148 to Arg-156, Lys-196 to Lys-215.
840561	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1281 as residues: Ser-21 to Phe-30.
840562	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1282 as residues: Gln-33 to Arg-41, Tyr-66 to Glu-71, Thr-112 to Gly-118, Thr-141 to Gly-148, Thr-160 to Cys-168, Arg-171 to Gly-177, Thr-180 to Pro-191, Glu-217 to Asp-225, Asp-236 to Lys-243.
840564	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1283 as residues: Val-13 to Pro-19, Gln-34 to Gly-39.
840600	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1285 as residues: Leu-26 to Ile-39.
840620	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1288 as residues: Ser-17 to Ser-26, His-32 to Gly-42, Thr-78 to Gln-83, Asp-130 to Leu-136, Arg-158 to Pro-164.
840626	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1290 as residues: Phe-7 to Tyr-13, Pro-19 to Ala-35, Asp-87 to Leu-96, Lys-98 to Glu-105, Glu-120 to Leu-133.
840638	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1291 as



	residues: Gly-8 to Leu-13, Gly-21 to Ser-31, Arg-45 to Arg-54.
840649	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1292 as residues: Asn-30 to Thr-37, Asp-44 to Lys-52, Ser-71 to Asp-80, Glu-127 to Glu-133, Arg-162 to Ala-173, Glu-191 to Leu-199.
840651	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1293 as residues: Gly-14 to Glu-38, Asn-90 to Lys-100, Lys-150 to Val-158, Ser-166 to Gly-175.
840681	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1295 as residues: Thr-25 to Gly-31, Pro-86 to Trp-97, Ser-132 to Phe-138.
840682	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1296 as residues: Arg-12 to Lys-19, Asn-30 to Gly-36, Asp-50 to Gly-57, Glu-64 to Thr-69, Thr-79 to Lys-91, Gln-110 to Thr-115, Arg-223 to Gln-229, Asp-255 to Asp-260, Arg-278 to Gly-287, Glu-294 to Gln-300, Glu-433 to Glu-451, Leu-474 to Glu-479, Asp-490 to Leu-498, Gln-519 to Asp-527, Tyr-566 to Asp-575.
840684	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1297 as residues: Pro-1 to Ala-9, Val-56 to Val-63, Gly-86 to Glu-91.
840697	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1298 as residues: Pro-9 to Arg-15, Pro-36 to Ser-42, Ser-65 to Phe-72, Gly-99 to Ser-105, Ala-122 to Phe-129.
840698	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1299 as residues: Thr-75 to Pro-84, His-94 to Met-99, Asp-149 to Ile-168, Asn-370 to Asn-375, Ser-384 to Lys-392, His-427 to Tyr-438.
840708	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1300 as residues: Ala-27 to Ser-36.
840714	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1301 as residues: Gly-1 to Gly-20, Arg-54 to His-59, Asn-89 to Leu-95, Ser-119 to Lys-125, Trp-127 to Cys-133, Gln-175 to Gln-185, Asp-213 to Lys-222, Pro-267 to Gln-275, Asp-306 to Asp-313, Thr-321 to Cys-331.
840716	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1302 as residues: Asn-40 to Thr-45, His-210 to Pro-215, Glu-369 to Thr-375, Lys-383 to Leu-397, Pro-438 to Ile-447, Pro-510 to Tyr-520, Arg-528 to Arg-533, Thr-549 to Thr-555.
840721	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1303 as residues: Arg-1 to Arg-7, Pro-29 to Lys-56, Asp-103 to Arg-108, Tyr-122 to Ser-127, Gly-219 to Glu-227, Asp-250 to Glu-255, Glu-294 to Pro-301, Ala-321 to Tyr-327, Arg-367 to Pro-373, Glu-396 to Asn-405, Gly-411 to Arg-418, Asn-433 to Lys-441.
840735	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1304 as residues: Glu-1 to Gly-11, Thr-20 to Asp-40, Gly-51 to Glu-61, Ala-64 to Leu-78, Leu-82 to Arg-94.
840738	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1305 as residues: Gln-26 to Asn-34.
840745	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1306 as residues: Gln-7 to Gly-12, Leu-60 to Pro-65, Arg-85 to Lys-99, Ser-132 to Pro-145, Pro-150 to Asp-155, Pro-183 to Asn-193, Arg-200 to Tyr-206.
840747	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1307 as residues: Gln-1 to Asp-15, Ile-35 to Glu-41, Leu-66 to Asn-71, Leu-73 to Pro-79, Gln-87 to Lys-94, Val-117 to Arg-123, Pro-144 to Tyr-150.
840756	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1308 as residues: Arg-8 to Gln-19, Arg-25 to Lys-38.
840776	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1309 as residues: Val-2 to Pro-10, Ser-28 to Ala-33, Pro-39 to Tyr-44, Thr-46 to Trp-55, Ser-64 to Ser-72, Ala-103 to Pro-109, Pro-111 to Gln-118.
840784	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1310 as residues: Pro-9 to Gly-20, Asn-32 to Leu-42, Asn-60 to Lys-70, Pro-76 to Gln-81, Glu-86 to Val-93, Arg-106 to Arg-111, Lys-176 to Asn-183.
840788	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1311 as residues: Ser-1 to Gln-8, Val-40 to Ser-49, Arg-105 to Lys-110.

840794	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1312 as residues: Arg-1 to Gln-14, Arg-43 to Glu-54.
840797	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1313 as residues: Gly-1 to Arg-9, Asn-31 to Asp-37, Arg-44 to Asn-53, Gly-62 to Lys-77, Thr-123 to Ile-137, Gly-389 to Thr-394, Lys-486 to Asn-493, Glu-512 to Phe-520, Met-555 to Lys-560, Leu-618 to Ser-623, Ile-698 to Glu-706, Gly-723 to Leu-730, Ala-773 to Gln-790.
840818	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1315 as residues: Pro-1 to Ile-12, Asp-30 to Tyr-35, Leu-38 to Pro-45, Lys-54 to Thr-60, Thr-75 to Leu-80, Asp-92 to Tyr-100, Ile-133 to Thr-138, Thr-194 to Glu-199, Asp-233 to Leu-239, Met-243 to Ala-251, Asp-254 to Glu-261.
840822	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1316 as residues: Val-100 to Tyr-106, Ala-127 to His-135, Gln-153 to Lys-158, Gly-214 to Glu-219, Gln-236 to His-244, Lys-253 to Tyr-258.
840846	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1318 as residues: Ala-20 to Thr-27, Glu-47 to Tyr-57, Tyr-87 to Lys-95, Pro-121 to Ala-127, Pro-208 to Ala-224.
840848	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1319 as residues: Arg-77 to Asn-82, Glu-119 to Arg-124, Gln-156 to Thr-162, Lys-209 to Lys-215.
840860	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1320 as residues: Ile-27 to Asp-41, Glu-43 to Ala-58, Glu-149 to Glu-154, Lys-158 to Ile-165, Glu-167 to Gly-189, Glu-242 to Phe-247, Arg-259 to Phe-268, Ile-283 to Val-291, Thr-295 to Thr-307, Glu-328 to Asp-338, Asp-372 to Gly-387.
840871	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1322 as residues: Gly-31 to Tyr-38, Leu-40 to Leu-45, Pro-203 to Trp-208.
840874	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1323 as residues: Ala-23 to Gly-28.
840878	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1324 as residues: Thr-40 to Glu-46, Pro-69 to Arg-76, Glu-108 to Asp-150.
840880	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1325 as residues: Ser-5 to Lys-14, Phe-32 to Gln-37.
840884	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1326 as residues: Leu-4 to Ser-10.
840926	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1328 as residues: Met-6 to Thr-15, Ser-17 to Phe-37, Ser-148 to Lys-154, Lys-260 to Phe-276, Glu-285 to Ile-292, Lys-410 to Asp-424.
840932	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1329 as residues: Tyr-75 to Pro-83, Ile-181 to Gln-191, Glu-267 to Leu-275, Met-301 to Ala-307, Phe-322 to Gln-328, Met-371 to Gly-381, Gln-458 to Leu-463, Glu-474 to Lys-480, Lys-551 to Ser-558.
840940	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1330 as residues: Ser-26 to Thr-34, Thr-80 to Lys-88.
840947	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1331 as residues: Ile-1 to Arg-11, Pro-19 to Gln-46, Ala-55 to Pro-62, Cys-65 to Cys-82, Lys-93 to Pro-108.
840964	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1333 as residues: Ser-41 to Cys-46.
840979	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1334 as residues: Tyr-10 to His-27, Tyr-31 to Arg-41, Thr-44 to Leu-61, Cys-68 to Phe-73, Lys-98 to Glu-106, Gln-132 to Val-142, Glu-184 to Leu-191.
840984	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1335 as residues: Arg-38 to Gln-48, Met-137 to Asn-144, Gln-167 to Gln-172, Lys-182 to Gln-189, Gln-196 to Glu-206, Ile-210 to Glu-223, Gln-225 to Arg-246, Glu-250 to Thr-269, Gln-296 to Ile-318, Arg-323 to Glu-328, Tyr-337 to Lys-343, Glu-349 to Thr-357, Ser-393 to Glu-403, Arg-405 to Ile-427, Arg-431 to Glu-442, Leu-446 to Lys-473, Glu-475

	to Leu-486, Ile-488 to Asp-503, Ser-505 to Arg-623, Ala-625 to Asn-631, His-634 to Trp-792, Gly-799 to Gly-870, Arg-872 to Glu-929, Ser-931 to Pro-954, Ala-957 to Ala-977, Glu-982 to Trp-1000.
840986	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1336 as residues: Asp-41 to Tyr-51.
840988	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1337 as residues: Pro-17 to Leu-31, Ser-95 to Val-100, Lys-123 to Gly-129.
840990	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1338 as residues: Met-9 to Glu-16, Glu-41 to Trp-47, Arg-55 to Glu-62, Asp-135 to Ile-146, Gly-154 to Gly-160, Met-207 to Phe-214, Ser-245 to Lys-252, Gln-282 to Gln-288.
841009	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1340 as residues: Glu-12 to Thr-27, Met-45 to Asn-52, Tyr-79 to Thr-87, Asp-97 to Gly-102, Met-112 to Asp-120, Pro-141 to Tyr-155.
841012	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1341 as residues: Lys-36 to Ile-44, Arg-49 to Lys-69.
841016	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1342 as residues: Cys-75 to His-82, Asp-126 to Tyr-135, Pro-144 to Tyr-155, Gly-179 to Trp-198, Tyr-201 to Met-208, Pro-226 to Lys-234, Gln-249 to Asp-267.
841017	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1343 as residues: Gln-1 to Trp-19.
841021	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1344 as residues: Glu-58 to Gly-63, Leu-75 to Leu-82.
841032	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1345 as residues: Pro-1 to Gly-13, Pro-30 to Ser-57, Gln-61 to Thr-77, Arg-82 to Thr-88, Pro-100 to Lys-105, Gly-119 to Gly-126.
841051	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1346 as residues: Asn-1 to Lys-6, Thr-16 to Glu-21, Asn-45 to Ser-58, Asp-68 to Ser-75.
841064	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1347 as residues: Asp-53 to Pro-58, Glu-78 to Lys-85, Pro-95 to Arg-102, Ser-142 to Arg-148, Lys-209 to Arg-214, Lys-241 to Gly-246, Ser-287 to Leu-292, Lys-307 to Val-313, Arg-389 to Gln-394.
841069	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1348 as residues: Thr-1 to Trp-14, Lys-27 to Leu-44, Glu-59 to Arg-73, Lys-87 to Phe-95, Pro-160 to Asn-166, Leu-212 to Ile-220, Arg-236 to Asp-243.
841072	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1349 as residues: Pro-7 to Arg-12, Phe-71 to Gln-76, Arg-82 to Asp-98, Ala-108 to Glu-128.
841078	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1350 as residues: Arg-32 to Ala-39.
841080	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1351 as residues: Glu-1 to Gly-7, Glu-25 to Gly-33, Ala-54 to Phe-60, Gly-64 to Gln-108, Glu-116 to Ser-122, Pro-130 to Asn-138, Gln-141 to Lys-153, Arg-164 to Ser-172, Leu-186 to Met-194, Pro-197 to Tyr-205, Asp-218 to Lys-229, Thr-236 to Ser-246, Ala-259 to Trp-266, Pro-281 to Pro-287, Cys-291 to Gln-298.
841092	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1353 as residues: Glu-45 to Lys-50.
841095	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1354 as residues: Lys-1 to Ser-19, Gly-33 to Gly-63, Gly-77 to Pro-89, Ser-164 to Ser-180, Ser-233 to Lys-238, Lys-267 to Leu-286.
841096	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1355 as residues: Gly-5 to Leu-12, Tyr-18 to Asp-25, Ile-88 to Ala-125, Ser-129 to Tyr-141, Gln-191 to Gln-196, Thr-290 to Asn-296, Thr-301 to Thr-309, Leu-360 to Ala-365, Leu-367 to Gly-378, Pro-398 to Gly-418, Pro-443 to Gly-454.
841102	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1356 as residues: Ser-61 to Leu-71.
841108	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1358 as residues: Ala-8 to Leu-20, Lys-27 to Arg-33, Arg-40 to Ala-50, Asp-77 to Glu-84,

	Asn-99 to Gly-109.
841119	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1360 as residues: Lys-6 to Ala-14, Ile-68 to Asn-73, Val-84 to Leu-90, Glu-110 to Val-116, Leu-182 to Gly-190, Tyr-264 to Phe-270, Ile-300 to Lys-306, Pro-354 to Glu-367.
841124	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1361 as residues: Ser-21 to Thr-26.
841143	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1363 as residues: Thr-1 to Lys-9, Pro-20 to Gly-27, Gly-29 to Gly-52, Arg-54 to Gly-61, Gly-69 to Gly-75, Ser-79 to Gly-96, Val-130 to Arg-135, His-207 to Asp-212, Val-296 to Leu-310, Arg-327 to Asn-334.
841148	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1364 as residues: Pro-1 to Met-43, Pro-55 to Ala-66, Pro-118 to Glu-128, Arg-181 to Lys-192, Tyr-197 to Thr-207, Trp-278 to Cys-284, Arg-334 to Asp-349.
841155	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1367 as residues: Gly-9 to Arg-24, Glu-69 to Met-74, Leu-86 to Leu-92, Asp-95 to Arg-115.
841163	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1370 as residues: Gly-29 to Gly-35, Ala-37 to Ala-48, Arg-97 to Thr-102, Arg-114 to Leu-119, Lys-144 to Lys-155.
841169	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1371 as residues: Ala-31 to Thr-69, Pro-90 to Pro-95, Pro-117 to Trp-126, Pro-128 to Arg-136.
841172	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1372 as residues: Gly-17 to Arg-35, His-76 to Pro-90, Pro-92 to Cys-103.
841174	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1373 as residues: Arg-1 to Arg-8, Arg-14 to Phe-19.
841179	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1374 as residues: Leu-4 to Met-10, Leu-17 to Tyr-36, Arg-38 to Asp-63, Tyr-82 to Glu-90, Pro-97 to Gly-134, Arg-137 to Pro-148, Thr-160 to Lys-171, Tyr-183 to Asn-228, Gln-249 to Asn-258, Arg-263 to Glu-271, Arg-277 to Gln-296, Phe-298 to Asp-320, Glu-322 to Lys-329, Thr-337 to Thr-343, Glu-356 to Arg-363, Gly-371 to Asp-384.
841183	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1375 as residues: His-1 to Ser-27, Arg-60 to Arg-73, Arg-96 to Asp-124, Asp-131 to Gly-143, Lys-145 to Glu-150.
841186	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1376 as residues: Leu-7 to Val-18, Ser-27 to Pro-57, Arg-124 to Thr-135, Pro-212 to Ser-230, Gly-282 to Lys-287, Lys-441 to Lys-448.
841204	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1377 as residues: Lys-29 to Arg-35, Glu-81 to Arg-87, Ala-251 to Glu-261, Thr-266 to Gly-271, Thr-289 to Glu-295, Gly-328 to Tyr-334, Phe-432 to Lys-438, Asn-440 to Trp-458.
841206	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1378 as residues: Val-17 to Pro-25, Thr-55 to Asp-70, Lys-75 to Leu-81.
841207	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1379 as residues: Pro-9 to Glu-15, Arg-22 to Trp-32, Ser-54 to Glu-62, Asn-92 to Gly-103.
841211	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1380 as residues: Arg-7 to Gly-12, Met-42 to Ser-58, Gln-65 to Asn-73, Glu-91 to Ala-99, Pro-103 to Tyr-109, Arg-174 to Ala-179, His-189 to Gln-196, Asn-208 to Pro-219.
841225	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1381 as residues: Ala-32 to Ala-40, Glu-93 to Phe-103, Lys-173 to Thr-189.
841237	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1383 as residues: Arg-2 to Gln-12, Lys-76 to Ala-86, Tyr-155 to Lys-163, Glu-228 to Leu-234, Lys-263 to Lys-273, Ile-286 to Lys-296.
841241	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1384 as residues: Asp-41 to Ile-52, Thr-59 to Lys-64, Glu-75 to Asn-89, Thr-99 to Thr-105.
841259	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1385 as residues: His-1 to Cys-22, Pro-24 to Pro-30, Tyr-84 to Ser-90, Ser-108 to Glu-118, Val-126 to Arg-143, Asp-175 to Gln-181, Ser-217 to Gly-224, Cys-262 to Cys-270.

	Tyr-296 to Glu-302, Thr-317 to Thr-324, Gln-341 to Gln-348, Trp-394 to Pro-399.
841260	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1386 as residues: Ala-25 to Glu-32, Ala-48 to Phe-53, Ser-69 to Ser-76, Asp-80 to Glu-86, Ser-125 to Ser-132, Ser-168 to Glu-179, Asn-201 to Ala-206, Lys-216 to Ile-246, Met-259 to Asn-272, Tyr-277 to Gln-287.
841264	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1387 as residues: Met-34 to Gly-50, Asp-69 to Trp-90, Asp-99 to Lys-107, Val-164 to Thr-170.
841311	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1389 as residues: Arg-4 to Val-15.
841313	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1390 as residues: His-6 to Gly-16, Gly-60 to Pro-95, Pro-125 to Gly-131, Gly-138 to Ala-147, Gln-173 to Glu-178.
841322	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1392 as residues: Lys-6 to Arg-23, Ser-74 to Arg-86, Lys-116 to Lys-122, Ser-127 to His-133, Ser-269 to Pro-275, Glu-344 to Phe-350, Gly-356 to His-362.
841331	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1393 as residues: Ser-45 to Lys-67, Asp-155 to Asp-172, Gln-193 to Ile-199, Gln-271 to Glu-285.
841332	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1394 as residues: Glu-8 to Ser-13, Lys-20 to Glu-27, Arg-81 to Ser-94, Thr-147 to Ile-154, Asn-200 to Glu-212, Asn-235 to Gly-244, Leu-433 to Thr-439, Pro-444 to Asn-455, Ser-470 to Asp-476, Ser-492 to Met-499, Glu-535 to Pro-547, Glu-703 to Thr-709, Glu-719 to Thr-726, Asn-802 to Leu-807, Asn-820 to Arg-825, Lys-830 to Tyr-836, Thr-838 to Thr-850, Ser-882 to Ser-894, Lys-944 to Gly-952, Gly-969 to Val-977, Glu-984 to Asn-990, Arg-996 to Lys-1001, Pro-1032 to Leu-1039, Thr-1050 to Gly-1058, Val-1103 to Arg-1108, Pro-1160 to His-1169, Tyr-1180 to Ser-1187, Glu-1211 to Ser-1217, Pro-1277 to Leu-1282.
841338	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1395 as residues: Ser-13 to Ser-18, Phe-48 to Ser-54.
841345	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1396 as residues: Trp-83 to Thr-89, Ser-135 to Asn-140, Ser-185 to Cys-190, Tyr-209 to Glu-220, Val-224 to Glu-232, Leu-258 to Asn-263, Ser-306 to Asn-312, Thr-319 to Glu-327, Thr-365 to Ile-373, Gly-417 to Cys-429, Lys-439 to Val-445, Lys-464 to Leu-469, Leu-477 to Asn-485, Arg-546 to Val-554, Glu-598 to Gly-607, Pro-634 to Ser-639, Asn-730 to Ala-746, Lys-812 to Gln-817, Glu-819 to Lys-835, Leu-867 to Asn-875, Leu-902 to Arg-910.
841349	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1397 as residues: Asp-13 to Arg-18, Pro-36 to Arg-43, Gly-66 to Ser-74, Gly-87 to Lys-92, Asp-110 to Glu-115.
841417	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1399 as residues: Leu-102 to Ile-111, Pro-131 to Ile-337, Thr-339 to Asp-376.
841632	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1401 as residues: Arg-13 to Gly-40, Arg-46 to Glu-52, Gln-55 to Lys-69.
841771	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1403 as residues: Pro-22 to Gly-30, Asp-45 to Gln-56, Ser-67 to Ser-73.
841827	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1404 as residues: Thr-1 to Ser-20.
841835	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1405 as residues: Tyr-5 to Lys-13, Cys-52 to Arg-61, Cys-85 to Ala-91, Gly-122 to Asn-127.
842259	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1406 as residues: Pro-16 to Gly-23, Glu-37 to Pro-45, Gly-52 to Ser-57.
842463	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1407 as residues: Cys-74 to Tyr-79.
842595	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1408 as residues: Pro-93 to Ala-105, Ser-133 to Ser-142, Arg-150 to Glu-155, Lys-220 to Trp-

	226, Glu-257 to Lys-271, Gln-280 to Leu-289.
842722	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1409 as residues: Glu-9 to Arg-20, Ser-48 to Lys-56, Ile-69 to Glu-81, Pro-83 to Lys-89, Lys-94 to Ile-99, Pro-104 to Gly-110, Glu-116 to Asp-133, Ile-140 to Ser-154, Gln-206 to His-217, Pro-219 to Leu-231, Arg-237 to Lys-243, Gln-247 to Pro-256, Leu-271 to Thr-283, Lys-289 to Lys-294, Ser-338 to Lys-355, Gly-375 to Thr-381, Ser-428 to Pro-454, Gly-460 to Gln-467, Lys-480 to Lys-488.
842818	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1411 as residues: Ala-25 to Ala-30, Lys-32 to Ala-51, Gln-61 to Ala-68, Glu-83 to Lys-91, Phe-99 to Glu-105, Glu-123 to Gly-129.
843251	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1412 as residues: Pro-30 to Ser-40, Lys-47 to Thr-52, Val-59 to Pro-64, Lys-129 to Arg-134, Leu-169 to Asp-177.
843422	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1413 as residues: Thr-9 to Lys-20, Lys-25 to Cys-31, Pro-33 to Tyr-42, Asn-76 to Lys-84, Leu-102 to Trp-112.
843784	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1414 as residues: Leu-16 to Thr-24, Glu-41 to Gln-47, Lys-64 to Cys-72, Thr-87 to Ser-100, Pro-130 to Asn-143, Thr-163 to Asp-170.
844017	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1415 as residues: Leu-11 to Ile-17, Leu-30 to Met-45.
844138	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1416 as residues: Lys-19 to Thr-28, Arg-47 to Gln-52, Leu-73 to Leu-81, Asp-122 to Phe-131, Ala-135 to Ser-148, Pro-155 to Asp-163, Ser-184 to His-191, Leu-219 to Asn-225, Asp-238 to Thr-248, Pro-253 to Cys-259, Cys-356 to His-368, Ser-426 to Gly-435, Pro-467 to Cys-478, Glu-504 to Cys-509, His-553 to Gly-568, Ala-581 to Cys-586, Ala-595 to Cys-600, Arg-602 to Trp-608.
844194	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1418 as residues: Pro-23 to Arg-31, Gln-79 to Gln-85, Cys-93 to Cys-107, Pro-216 to Leu-222.
844394	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1419 as residues: Arg-1 to Phe-11.
844450	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1420 as residues: Ser-37 to Trp-43, Pro-47 to Thr-55, Arg-60 to Lys-69, Tyr-125 to His-131, Pro-187 to Lys-195, Gly-346 to Lys-351.
844535	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1422 as residues: Asp-8 to Ala-18, Ser-47 to Ala-52, Thr-62 to Arg-69, Pro-119 to Asp-126, Trp-164 to Thr-170, Ala-206 to Ala-213, Pro-230 to Gly-235, Lys-304 to Lys-314, Lys-341 to Val-347, Tyr-387 to Thr-398.
844644	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1423 as residues: Ala-9 to Asp-16, Asn-78 to Tyr-86.
844653	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1424 as residues: Arg-1 to Gly-8, Ala-30 to Gln-36.
844796	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1426 as residues: His-12 to His-22.
844812	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1427 as residues: Gly-281 to Arg-290, Ala-349 to Ser-355, Glu-378 to Asp-388.
844894	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1428 as residues: Pro-2 to Phe-8, Ser-13 to Ala-34, Pro-37 to Phe-43, Lys-63 to Gly-73, Cys-88 to Asp-93, Gly-98 to Trp-103, Cys-273 to Ile-287, Ile-290 to Ser-296.
845361	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1429 as residues: Met-10 to Ile-21, Glu-108 to Lys-122, Lys-272 to Gly-280, Gly-298 to Lys-304, Trp-364 to Lys-369.
845620	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1430 as residues: Thr-62 to Ala-67, Leu-96 to Glu-101, Cys-184 to Trp-190.
845639	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1431 as residues: Arg-41 to Arg-48, Met-72 to Val-79, Gln-81 to Trp-89, Ala-96 to Asp-101,

	Arg-110 to Gly-118, Asn-126 to Arg-135, Ala-144 to Asp-149, Leu-199 to Lys-213, Gln-245 to Glu-256, Arg-261 to Thr-267.
845660	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1432 as residues: Gly-5 to Leu-17, Arg-19 to Arg-29, Pro-36 to Arg-50, Arg-60 to Pro-67, Gln-133 to Leu-150, Gln-168 to Phe-187, Pro-189 to Gln-194, Asp-240 to Gly-251, Thr-308 to Cys-317, Val-325 to Glu-331, Leu-354 to Pro-369, Lys-381 to Cys-388, Arg-410 to Phe-417.
845720	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1433 as residues: Thr-1 to Glu-11, Arg-21 to Pro-27, Pro-44 to His-49, Glu-56 to Leu-69, Ala-74 to Gly-80, Phe-82 to Pro-87.
845897	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1435 as residues: Gly-1 to Ser-9, Gly-31 to Ser-38, Arg-52 to Val-68, Leu-71 to Glu-84.
845922	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1436 as residues: Asn-1 to Pro-6, Pro-29 to Gln-36, Glu-95 to Arg-100, Pro-150 to Met-157, Ser-272 to Tyr-278, Gly-289 to Arg-294, Lys-397 to Ser-403.
846040	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1438 as residues: Cys-6 to Ser-16, Glu-52 to Tyr-58, Asn-144 to Lys-153.
846073	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1439 as residues: Arg-6 to Thr-16, Ile-43 to Gln-48, Leu-131 to Gly-139, Gly-147 to Asp-155, Asp-191 to Asp-198, Gly-204 to Thr-214.
846257	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1440 as residues: Lys-24 to Phe-44, Arg-58 to Gly-64, Ser-69 to Val-75, Lys-83 to Leu-90, Lys-93 to Glu-106.
HTXPN06R	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1441 as residues: Gly-1 to His-8.
HWAFU16R	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1443 as residues: Ile-29 to Lys-34.
HOEMT44R	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1445 as residues: Asp-73 to Lys-79.
HE2OW04R	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1446 as residues: Cys-1 to Asn-6, Met-41 to Thr-51, Lys-77 to Thr-82.
HFCFG25R	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1447 as residues: Lys-29 to Ile-37, Arg-42 to Lys-47.
HAPQP94R	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1448 as residues: Pro-18 to Arg-23, Ala-43 to Ser-48.
H2CBI37R	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1449 as residues: Gly-5 to Lys-19, Phe-26 to Trp-31.
HCRNC25R	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1451 as residues: Leu-2 to Asn-8.
H2LAY26R	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1453 as residues: Pro-20 to His-36.
HAPQA06R	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1454 as residues: Tyr-15 to Ala-22, Ser-68 to Gly-74.
HBGOK18R	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1456 as residues: Gly-1 to Tyr-6, Asp-40 to Thr-47, Lys-91 to Glu-97.
HTWKF26R	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1458 as residues: Gly-31 to Gly-39.
HTAHR89R	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1459 as residues: Asp-73 to Gly-78.
HOELC27R	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1461 as residues: Asn-19 to Gln-25, Arg-33 to Ala-42, Pro-92 to Lys-99.
HWLVW62R	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1463 as residues: Lys-6 to Phe-13, His-25 to Ser-30, Glu-35 to Ala-41, Pro-57 to Gly-62.
HFKHD94R	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1465 as residues: Leu-1 to Gly-6, Pro-29 to Gly-42, Lys-52 to Gly-62.
HOFOA89R	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1467 as

	residues: Ala-20 to Lys-29, Arg-48 to Ile-56.
HCROL58R	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1470 as residues: Lys-1 to Ser-16.
HCHMV24R	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1473 as residues: Gly-4 to Lys-10, Gln-36 to Glu-41.
HCHPT49R	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1474 as residues: Gly-4 to Lys-10, Gln-36 to Glu-41, Arg-61 to Arg-70.
HCHPF59R	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1477 as residues: Arg-10 to Lys-22.
HS2IA81R	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1478 as residues: Gly-4 to Lys-10, Gln-36 to Glu-41, Arg-61 to Arg-76.
HCRNC17R	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1479 as residues: Gly-4 to Lys-10, Gln-36 to Glu-41, Arg-61 to Arg-76, Lys-107 to Pro-112.
HISDJ39R	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1480 as residues: Gly-4 to Lys-10, Gln-36 to Glu-41, Arg-61 to Arg-76.
HASCG71R	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1482 as residues: Lys-6 to Ile-13.
HOEMO43R	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1483 as residues: Lys-31 to Gln-43.
HSYDG18R	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1486 as residues: Pro-1 to Glu-7, Asp-42 to Gly-47, Leu-61 to Glu-69, Lys-97 to Ile-107, Asp-115 to Gly-120.
HACAC47R	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1490 as residues: Ala-18 to Asp-26.
HLQFY41R	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1491 as residues: Val-11 to Asp-16, Glu-46 to Arg-51, Pro-55 to Lys-61, Lys-82 to Val-87.
HOFMO83R	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1492 as residues: Thr-31 to Asp-39, Thr-52 to Gly-60.
HFTDR22R	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1493 as residues: Glu-1 to Trp-13.
HOEKC39R	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1495 as residues: Tyr-25 to Phe-32.
HOSNR06R	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1498 as residues: Thr-1 to Tyr-7.
HCQDL20R	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1499 as residues: Ser-12 to His-21.
HFKHD49R	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1503 as residues: Ala-42 to Glu-68.
H6EAQ15R	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1506 as residues: Ala-1 to Leu-9.
HCFLM34R	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1507 as residues: Lys-7 to Thr-13, Asp-24 to Thr-30, Gly-39 to Glu-52, Leu-70 to Ile-78.
HKIXL19R	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1510 as residues: Thr-2 to Asn-12, Gly-14 to Arg-24.
HAJRB09R	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1512 as residues: Pro-1 to Glu-8, Ala-10 to Gly-26.
HAPNI86R	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1513 as residues: Glu-53 to Ser-59, His-121 to Gln-130.
HAPRJ22R	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1515 as residues: Gly-49 to Glu-64, Phe-76 to Thr-81.
HADGE45R	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1518 as residues: Arg-1 to Gln-26, Phe-59 to Lys-68.
HTXPN11R	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1519 as residues: Asp-1 to Lys-8, Asp-35 to Glu-41.
HCDBN37R	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1520 as residues: Cys-1 to Leu-15.



HABGF46R	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1527 as residues: Arg-11 to Arg-20, Asn-42 to Pro-57, Arg-64 to Ser-81.
HOELC15R	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1528 as residues: His-8 to Gly-18, Gln-56 to Arg-61.
H2LAR26R	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1529 as residues: Glu-11 to Asn-16, Lys-38 to Glu-43, Ala-62 to Asp-67, Asp-80 to Ser-101.
H2LAV85R	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1530 as residues: Pro-14 to Thr-25, Asp-89 to Gln-102, Ile-121 to Thr-131.
HBSDC92R	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1531 as residues: Arg-1 to Leu-11.
HUTHN01R	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1532 as residues: Pro-34 to Ser-42, Cys-82 to Lys-89.
H2LAW03R	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1533 as residues: Arg-120 to Arg-127.
HOEMO60R	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1534 as residues: Pro-6 to Arg-11, Phe-18 to Asn-23, Leu-36 to Thr-41.
HOELF72R	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1537 as residues: Arg-1 to Pro-14, Gln-47 to Cys-52.
HAPNX59R	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1538 as residues: Cys-19 to Ser-25, Asp-28 to Trp-34, Lys-71 to Trp-76, Glu-112 to Lys-120.
HBJS17R	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1539 as residues: His-14 to Glu-26.
H2CBN02R	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1542 as residues: Ala-1 to Pro-9, Arg-20 to Val-25.
H2CBV68R	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1543 as residues: Pro-41 to Asp-46, Leu-56 to Lys-61, Ala-72 to Thr-83, Lys-100 to Asn-106, Leu-125 to Thr-133.
H6EDK07R	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1544 as residues: Glu-32 to Glu-40, Val-45 to Thr-51, Pro-61 to Arg-67.
H2CBN54R	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1547 as residues: Cys-36 to Tyr-44, Glu-55 to Asp-61, Arg-79 to Pro-84, Asp-89 to Pro-105, Cys-108 to Ala-118, Lys-126 to Gly-142.
HWHPX50R	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1549 as residues: Pro-35 to Tyr-41.
HAPQD84R	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1550 as residues: Lys-32 to Glu-39.
HAMGQ78R	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1554 as residues: Arg-46 to Arg-60, Glu-69 to Gly-78.
HODEV64R	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1555 as residues: Glu-1 to Gly-27, Asn-34 to Phe-48, Gly-63 to Gly-68.
HOEMK78R	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1558 as residues: Asp-27 to Gly-34, Ser-41 to Glu-49, Val-55 to Gln-62.
H2CBD13R	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1559 as residues: Ile-17 to His-22, Ser-24 to Arg-29.
HCFMU61R	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1560 as residues: Ser-10 to Asp-20, Leu-22 to Pro-36, Ser-42 to Lys-57, Gln-102 to Glu-110.
HOSNE94R	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1561 as residues: Arg-1 to Glu-6, Asp-74 to Ser-79, Asp-122 to Thr-127.
HHBEF47R	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1563 as residues: Arg-25 to His-31, Ala-50 to Ala-55.
HOSNR67R	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1566 as residues: Val-56 to Cys-61, Thr-108 to Gln-122, Gln-125 to Lys-131, Glu-140 to Leu-146.
H2LAV92R	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1567 as residues: Leu-3 to Ala-10, Pro-12 to Gly-21, Pro-32 to Pro-38, Ala-58 to Lys-64, Lys-67 to Val-75, Asp-92 to Leu-103.

HCLBZ27R	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1570 as residues: Asp-12 to Glu-18, Ala-22 to Ile-28, Ala-48 to Gly-60.
H2LAV11R	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1571 as residues: Thr-5 to Thr-14, Arg-20 to His-25, Arg-35 to Gly-40, Lys-58 to Arg-66, His-101 to Ser-107, Arg-111 to Lys-125.
HOEMJ56R	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1573 as residues: Lys-27 to Tyr-48.
HDPLP40R	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1576 as residues: Gly-1 to Cys-24, Cys-27 to Gly-43, Ala-46 to Trp-54, Ala-56 to Arg-68, Phe-83 to Arg-93.
HABAD57R	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1578 as residues: Gly-3 to Gln-16, Pro-36 to Ala-41.
H2CBL68R	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1581 as residues: Pro-19 to Val-24, Thr-31 to Gln-38, His-103 to Lys-114, Arg-129 to Leu-137, Pro-139 to Ser-146.
HNTNE17R	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1582 as residues: Val-8 to Lys-15, Tyr-25 to Asn-35, Lys-48 to Lys-53, Leu-77 to Asn-87, Asp-103 to Glu-108.
HBJLR37R	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1583 as residues: Asn-1 to His-11, Pro-82 to Glu-89, Pro-91 to Asp-96, Arg-103 to Met-109.
HOSNG20R	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1584 as residues: Thr-50 to Lys-55.
HBGNY11R	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1586 as residues: Thr-10 to Trp-15, Leu-24 to Ala-30, Leu-32 to Glu-38, Asn-41 to Ala-59, Arg-81 to Asp-89, Lys-104 to Lys-111.
HOEKC80R	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1587 as residues: Pro-49 to Phe-55, Gly-82 to Gly-88.
HFCE53R	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1589 as residues: Thr-12 to Leu-18.
HWAFE36R	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1592 as residues: Glu-2 to Ile-9, Glu-34 to Lys-42.
HTXPF20R	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1594 as residues: Gly-4 to Thr-13.
HCRMD09R	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1595 as residues: Thr-2 to Asn-10, Glu-22 to Gln-30, Ser-58 to Gln-80, Gln-88 to Phe-96, Thr-99 to Tyr-104, Lys-110 to Asp-115.
HAJRB47R	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1596 as residues: Trp-18 to Ser-26, Asp-91 to Trp-99.
HAHCR61R	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1603 as residues: Ser-17 to Cys-25.
HAPQK19R	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1609 as residues: Arg-1 to Lys-10, Ser-15 to Tyr-22, Gly-25 to Leu-31.
HBGOK25R	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1615 as residues: Thr-38 to Trp-45, Pro-63 to Gln-70, Pro-78 to Gln-85.
HBJKI05R	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1619 as residues: Pro-43 to Trp-50.
HBLGD42R	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1621 as residues: Pro-17 to Pro-27, Pro-32 to Tyr-38, Ala-44 to Pro-49.
HCHAK80R	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1627 as residues: Gln-3 to His-13, Gly-48 to Gly-55.
HCHMW79R	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1628 as residues: Ser-16 to His-21, Ala-29 to Thr-35.
HCHOB92R	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1629 as residues: Lys-20 to Lys-28, Ser-53 to Leu-60.
HCLBO01R	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1630 as residues: Leu-1 to Leu-18.

HCRPC63R	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1633 as residues: Glu-1 to Arg-28.
HCUDC51R	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1634 as residues: Pro-22 to Gly-32, Trp-67 to Lys-81.
HDPFI40R	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1635 as residues: Tyr-1 to Phe-6, Pro-9 to Asn-22, Arg-30 to Ala-38, Pro-47 to Lys-69.
HDPRZ54R	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1637 as residues: Gly-1 to Ala-8.
HFAUO64R	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1640 as residues: Asn-7 to Lys-29.
HJMAU64R	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1645 as residues: Leu-58 to Tyr-69.
HKBAC48R	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1647 as residues: Ser-16 to His-46, Arg-49 to Thr-58.
HKBAD57R	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1648 as residues: Thr-23 to Ser-30.
HODAY16R	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1653 as residues: Pro-15 to Thr-20.
HOEMO27R	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1655 as residues: Ala-7 to Ser-12.
HOEMO62R	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1656 as residues: Ile-3 to Lys-11.
HOENU53R	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1658 as residues: Lys-37 to Asn-44.
HOGAP33R	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1659 as residues: Gln-29 to Asp-35, Gln-43 to Thr-49.
HOSNF25R	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1661 as residues: Pro-29 to Arg-36.
HPIAC23R	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1663 as residues: Thr-62 to Thr-69.
HRAAD31R	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1664 as residues: Val-1 to Thr-6, Arg-64 to Arg-69.
HRADJ57R	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1666 as residues: Val-11 to Gln-16.
HROAX48R	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1667 as residues: Gly-7 to Thr-20.
HTWDH05R	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1670 as residues: Ala-5 to Lys-11, Arg-29 to Ser-36.
HUTHF75R	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1673 as residues: Lys-40 to Gly-47.
HWAFW07R	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1674 as residues: Phe-44 to Arg-49.
HWLLX91R	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1676 as residues: Gly-29 to Asp-34.
HMIAI78R	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1678 as residues: Lys-24 to Arg-29, Cys-34 to Ala-41.
HBGFJ39R	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1679 as residues: Leu-21 to Asp-38.
HAMHH32R	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1680 as residues: Ala-1 to Cys-10, Glu-15 to Gln-21.
HOSNE37R	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1683 as residues: Lys-17 to Thr-23.
HWAFE41R	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1684 as residues: Ser-3 to Lys-8, Trp-92 to Leu-97.

The present invention encompasses polypeptides comprising, or alternatively consisting of, an epitope of the polypeptide sequence shown in SEQ ID NO:Y, or an epitope of the polypeptide sequence encoded by the cDNA in the related cDNA clone contained in a deposited library or encoded by a polynucleotide that hybridizes to the complement of an epitope encoding sequence of SEQ ID NO:X, or an epitope encoding sequence contained in the deposited cDNA clone under stringent hybridization conditions, or alternatively, under lower stringency hybridization conditions, as defined supra. The present invention further encompasses polynucleotide sequences encoding an epitope of a polypeptide sequence of the invention (such as, for example, the sequence disclosed in SEQ ID NO:X), polynucleotide sequences of the complementary strand of a polynucleotide sequence encoding an epitope of the invention, and polynucleotide sequences which hybridize to this complementary strand under stringent hybridization conditions or alternatively, under lower stringency hybridization conditions, as defined supra.

The term "epitopes," as used herein, refers to portions of a polypeptide having antigenic or immunogenic activity in an animal, preferably a mammal, and most preferably in a human. In a preferred embodiment, the present invention encompasses a polypeptide comprising an epitope, as well as the polynucleotide encoding this polypeptide. An "immunogenic epitope," as used herein, is defined as a portion of a protein that elicits an antibody response in an animal, as determined by any method known in the art, for example, by the methods for generating antibodies described infra. (See, for example, Geysen et al., Proc. Natl. Acad. Sci. USA 81:3998- 4002 (1983)). The term "antigenic epitope," as used herein, is defined as a portion of a protein to which an antibody can immunospecifically bind its antigen as determined by any method well known in the art, for example, by the immunoassays described herein. Immunospecific binding excludes non-specific binding but does not necessarily exclude cross- reactivity with other antigens. Antigenic epitopes need not necessarily be immunogenic.

Fragments which function as epitopes may be produced by any conventional means. (See, e.g., Houghten, R. A., Proc. Natl. Acad. Sci. USA 82:5131-5135 (1985) further described in U.S. Patent No. 4,631,211.)

In the present invention, antigenic epitopes preferably contain a sequence of at  
5 least 4, at least 5, at least 6, at least 7, more preferably at least 8, at least 9, at least  
10, at least 11, at least 12, at least 13, at least 14, at least 15, at least 20, at least 25, at  
least 30, at least 40, at least 50, and, most preferably, between about 15 to about 30  
amino acids. Preferred polypeptides comprising immunogenic or antigenic epitopes  
are at least 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, or 100  
10 amino acid residues in length. Additional non-exclusive preferred antigenic epitopes  
include the antigenic epitopes disclosed herein, as well as portions thereof. Antigenic  
epitopes are useful, for example, to raise antibodies, including monoclonal antibodies,  
that specifically bind the epitope. Preferred antigenic epitopes include the antigenic  
epitopes disclosed herein, as well as any combination of two, three, four, five or more  
15 of these antigenic epitopes. Antigenic epitopes can be used as the target molecules in  
immunoassays. (See, for instance, Wilson et al., Cell 37:767-778 (1984); Sutcliffe et  
al., Science 219:660-666 (1983)).

Similarly, immunogenic epitopes can be used, for example, to induce  
antibodies according to methods well known in the art. (See, for instance, Sutcliffe  
20 et al., supra; Wilson et al., supra; Chow et al., Proc. Natl. Acad. Sci. USA 82:910-  
914; and Bittle et al., J. Gen. Virol. 66:2347-2354 (1985). Preferred immunogenic  
epitopes include the immunogenic epitopes disclosed herein, as well as any  
combination of two, three, four, five or more of these immunogenic epitopes. The  
polypeptides comprising one or more immunogenic epitopes may be presented for  
25 eliciting an antibody response together with a carrier protein, such as an albumin, to  
an animal system (such as rabbit or mouse), or, if the polypeptide is of sufficient  
length (at least about 25 amino acids), the polypeptide may be presented without a  
carrier. However, immunogenic epitopes comprising as few as 8 to 10 amino acids  
have been shown to be sufficient to raise antibodies capable of binding to, at the very  
30 least, linear epitopes in a denatured polypeptide (e.g., in Western blotting).

Epitope-bearing polypeptides of the present invention may be used to induce antibodies according to methods well known in the art including, but not limited to, in vivo immunization, in vitro immunization, and phage display methods. See, e.g., Sutcliffe et al., supra; Wilson et al., supra, and Bittle et al., J. Gen. Virol., 66:2347-2354 (1985). If in vivo immunization is used, animals may be immunized with free peptide; however, anti-peptide antibody titer may be boosted by coupling the peptide to a macromolecular carrier, such as keyhole limpet hemacyanin (KLH) or tetanus toxoid. For instance, peptides containing cysteine residues may be coupled to a carrier using a linker such as maleimidobenzoyl- N-hydroxysuccinimide ester (MBS), while other peptides may be coupled to carriers using a more general linking agent such as glutaraldehyde. Animals such as rabbits, rats and mice are immunized with either free or carrier- coupled peptides, for instance, by intraperitoneal and/or intradermal injection of emulsions containing about 100 µg of peptide or carrier protein and Freund's adjuvant or any other adjuvant known for stimulating an immune response. Several booster injections may be needed, for instance, at intervals of about two weeks, to provide a useful titer of anti-peptide antibody which can be detected, for example, by ELISA assay using free peptide adsorbed to a solid surface. The titer of anti-peptide antibodies in serum from an immunized animal may be increased by selection of anti-peptide antibodies, for instance, by adsorption to the peptide on a solid support and elution of the selected antibodies according to methods well known in the art.

As one of skill in the art will appreciate, and as discussed above, the polypeptides of the present invention, and immunogenic and/or antigenic epitope fragments thereof can be fused to other polypeptide sequences. For example, the polypeptides of the present invention may be fused with the constant domain of immunoglobulins (IgA, IgE, IgG, IgM), or portions thereof (CH1, CH2, CH3, or any combination thereof and portions thereof) resulting in chimeric polypeptides. Such fusion proteins may facilitate purification and may increase half-life in vivo. This has been shown for chimeric proteins consisting of the first two domains of the human CD4-polypeptide and various domains of the constant regions of the heavy or light

chains of mammalian immunoglobulins. See, e.g., EP 394,827; Traunecker et al., Nature, 331:84-86 (1988). Enhanced delivery of an antigen across the epithelial barrier to the immune system has been demonstrated for antigens (e.g., insulin) conjugated to an FcRn binding partner such as IgG or Fc fragments (see, e.g., PCT Publications WO 96/22024 and WO 99/04813). IgG Fusion proteins that have a disulfide-linked dimeric structure due to the IgG portion disulfide bonds have also been found to be more efficient in binding and neutralizing other molecules than monomeric polypeptides or fragments thereof alone. See, e.g., Fountoulakis et al., J. Biochem., 270:3958-3964 (1995).

10 Similarly, EP-A-O 464 533 (Canadian counterpart 2045869) discloses fusion proteins comprising various portions of constant region of immunoglobulin molecules together with another human protein or part thereof. In many cases, the Fc part in a fusion protein is beneficial in therapy and diagnosis, and thus can result in, for example, improved pharmacokinetic properties. (EP-A 0232 262.) Alternatively, 15 deleting the Fc part after the fusion protein has been expressed, detected, and purified, may be desired. For example, the Fc portion may hinder therapy and diagnosis if the fusion protein is used as an antigen for immunizations. In drug discovery, for example, human proteins, such as hIL-5, have been fused with Fc portions for the purpose of high-throughput screening assays to identify antagonists of hIL-5. (See, 20 D. Bennett et al., J. Molecular Recognition 8:52-58 (1995); K. Johanson et al., J. Biol. Chem. 270:9459-9471 (1995).)

Moreover, the polypeptides of the present invention can be fused to marker sequences, such as a peptide which facilitates purification of the fused polypeptide. In preferred embodiments, the marker amino acid sequence is a hexa-histidine peptide, such as the tag provided in a pQE vector (QIAGEN, Inc., 9259 Eton Avenue, Chatsworth, CA, 91311), among others, many of which are commercially available. 25 As described in Gentz et al., Proc. Natl. Acad. Sci. USA 86:821-824 (1989), for instance, hexa-histidine provides for convenient purification of the fusion protein. Another peptide tag useful for purification, the "HA" tag, corresponds to an epitope

derived from the influenza hemagglutinin protein. (Wilson et al., Cell 37:767 (1984).)

Thus, any of these above fusions can be engineered using the polynucleotides or the polypeptides of the present invention.

5 Nucleic acids encoding the above epitopes can also be recombined with a gene of interest as an epitope tag (e.g., the hemagglutinin ("HA") tag or flag tag) to aid in detection and purification of the expressed polypeptide. For example, a system described by Janknecht et al. allows for the ready purification of non-denatured fusion proteins expressed in human cell lines (Janknecht et al., Proc. Natl. Acad. Sci. USA 10 88:8972- 897 (1991)). In this system, the gene of interest is subcloned into a vaccinia recombination plasmid such that the open reading frame of the gene is translationally fused to an amino-terminal tag consisting of six histidine residues. The tag serves as a matrix binding domain for the fusion protein. Extracts from cells infected with the recombinant vaccinia virus are loaded onto Ni<sup>2+</sup> nitriloacetic acid-agarose column and histidine-tagged proteins can be selectively eluted with imidazole-containing 15 buffers.

Additional fusion proteins of the invention may be generated through the techniques of gene-shuffling, motif-shuffling, exon-shuffling, and/or codon-shuffling (collectively referred to as "DNA shuffling"). DNA shuffling may be employed to 20 modulate the activities of polypeptides of the invention, such methods can be used to generate polypeptides with altered activity, as well as agonists and antagonists of the polypeptides. See, generally, U.S. Patent Nos. 5,605,793; 5,811,238; 5,830,721; 5,834,252; and 5,837,458, and Patten et al., Curr. Opinion Biotechnol. 8:724-33 (1997); Harayama, Trends Biotechnol. 16(2):76-82 (1998); Hansson, et al., J. Mol. 25 Biol. 287:265-76 (1999); and Lorenzo and Blasco, Biotechniques 24(2):308- 13 (1998) (each of these patents and publications are hereby incorporated by reference in its entirety). In one embodiment, alteration of polynucleotides corresponding to SEQ ID NO:X and the polypeptides encoded by these polynucleotides may be achieved by DNA shuffling. DNA shuffling involves the assembly of two or more DNA 30 segments by homologous or site-specific recombination to generate variation in the



polynucleotide sequence. In another embodiment, polynucleotides of the invention, or the encoded polypeptides, may be altered by being subjected to random mutagenesis by error-prone PCR, random nucleotide insertion or other methods prior to recombination. In another embodiment, one or more components, motifs, sections,  
5 parts, domains, fragments, etc., of a polynucleotide encoding a polypeptide of the invention may be recombined with one or more components, motifs, sections, parts, domains, fragments, etc. of one or more heterologous molecules.

As discussed herein, any polypeptide of the present invention can be used to generate fusion proteins. For example, the polypeptide of the present invention, when  
10 fused to a second protein, can be used as an antigenic tag. Antibodies raised against the polypeptide of the present invention can be used to indirectly detect the second protein by binding to the polypeptide. Moreover, because secreted proteins target cellular locations based on trafficking signals, polypeptides of the present invention which are shown to be secreted can be used as targeting molecules once fused to other  
15 proteins.

Examples of domains that can be fused to polypeptides of the present invention include not only heterologous signal sequences, but also other heterologous functional regions. The fusion does not necessarily need to be direct, but may occur through linker sequences.

20 In certain preferred embodiments, proteins of the invention comprise fusion proteins wherein the polypeptides are N and/or C- terminal deletion mutants. In preferred embodiments, the application is directed to nucleic acid molecules at least 80%, 85%, 90%, 95%, 96%, 97%, 98% or 99% identical to the nucleic acid sequences encoding polypeptides having the amino acid sequence of the specific N- and  
25 C-terminal deletions mutants. Polynucleotides encoding these polypeptides are also encompassed by the invention.

Moreover, fusion proteins may also be engineered to improve characteristics of the polypeptide of the present invention. For instance, a region of additional amino acids, particularly charged amino acids, may be added to the N-terminus of the  
30 polypeptide to improve stability and persistence during purification from the host cell

or subsequent handling and storage. Also, peptide moieties may be added to the polypeptide to facilitate purification. Such regions may be removed prior to final preparation of the polypeptide. The addition of peptide moieties to facilitate handling of polypeptides are familiar and routine techniques in the art.

5

#### **Vectors, Host Cells, and Protein Production**

The present invention also relates to vectors containing the polynucleotide of the present invention, host cells, and the production of polypeptides by recombinant techniques. The vector may be, for example, a phage, plasmid, viral, or retroviral vector. Retroviral vectors may be replication competent or replication defective. In the latter case, viral propagation generally will occur only in complementing host cells.

The polynucleotides of the invention may be joined to a vector containing a selectable marker for propagation in a host. Generally, a plasmid vector is introduced in a precipitate, such as a calcium phosphate precipitate, or in a complex with a charged lipid. If the vector is a virus, it may be packaged in vitro using an appropriate packaging cell line and then transduced into host cells.

The polynucleotide insert should be operatively linked to an appropriate promoter, such as the phage lambda PL promoter, the E. coli lac, trp, phoA and tac promoters, the SV40 early and late promoters and promoters of retroviral LTRs, to name a few. Other suitable promoters will be known to the skilled artisan. The expression constructs will further contain sites for transcription initiation, termination, and, in the transcribed region, a ribosome binding site for translation. The coding portion of the transcripts expressed by the constructs will preferably include a translation initiating codon at the beginning and a termination codon (UAA, UGA or UAG) appropriately positioned at the end of the polypeptide to be translated.

As indicated, the expression vectors will preferably include at least one selectable marker. Such markers include dihydrofolate reductase, G418 or neomycin resistance for eukaryotic cell culture and tetracycline, kanamycin or ampicillin resistance genes for culturing in E. coli and other bacteria. Representative examples

of appropriate hosts include, but are not limited to, bacterial cells, such as *E. coli*, *Streptomyces* and *Salmonella typhimurium* cells; fungal cells, such as yeast cells (e.g., *Saccharomyces cerevisiae* or *Pichia pastoris* (ATCC Accession No. 201178)); insect cells such as *Drosophila* S2 and *Spodoptera* Sf9 cells; animal cells such as  
5 CHO, COS, 293, and Bowes melanoma cells; and plant cells. Appropriate culture mediums and conditions for the above-described host cells are known in the art.

Among vectors preferred for use in bacteria include pQE70, pQE60 and pQE-9, available from QIAGEN, Inc.; pBluescript vectors, Phagescript vectors, pNH8A, pNH16a, pNH18A, pNH46A, available from Stratagene Cloning Systems, Inc.; and  
10 ptrc99a, pKK223-3, pKK233-3, pDR540, pRIT5 available from Pharmacia Biotech, Inc. Among preferred eukaryotic vectors are pWLNEO, pSV2CAT, pOG44, pXT1 and pSG available from Stratagene; and pSVK3, pBPV, pMSG and pSVL available from Pharmacia. Preferred expression vectors for use in yeast systems include, but are not limited to pYES2, pYD1, pTEF1/Zeo, pYES2/GS, pPICZ, pGAPZ, pGAPZalph,  
15 pPIC9, pPIC3.5, pHIL-D2, pHIL-S1, pPIC3.5K, pPIC9K, and PAO815 (all available from Invitrogen, Carlsbad, CA). Other suitable vectors will be readily apparent to the skilled artisan.

Introduction of the construct into the host cell can be effected by calcium phosphate transfection, DEAE-dextran mediated transfection, cationic lipid-mediated  
20 transfection, electroporation, transduction, infection, or other methods. Such methods are described in many standard laboratory manuals, such as Davis et al., Basic Methods In Molecular Biology (1986). It is specifically contemplated that the polypeptides of the present invention may in fact be expressed by a host cell lacking a recombinant vector.

25 A polypeptide of this invention can be recovered and purified from recombinant cell cultures by well-known methods including ammonium sulfate or ethanol precipitation, acid extraction, anion or cation exchange chromatography, phosphocellulose chromatography, hydrophobic interaction chromatography, affinity chromatography, hydroxylapatite chromatography and lectin chromatography. Most

preferably, high performance liquid chromatography ("HPLC") is employed for purification.

Polypeptides of the present invention can also be recovered from: products purified from natural sources, including bodily fluids, tissues and cells, whether  
5 directly isolated or cultured; products of chemical synthetic procedures; and products produced by recombinant techniques from a prokaryotic or eukaryotic host, including, for example, bacterial, yeast, higher plant, insect, and mammalian cells. Depending upon the host employed in a recombinant production procedure, the polypeptides of the present invention may be glycosylated or may be non-glycosylated. In addition,  
10 polypeptides of the invention may also include an initial modified methionine residue, in some cases as a result of host-mediated processes. Thus, it is well known in the art that the N-terminal methionine encoded by the translation initiation codon generally is removed with high efficiency from any protein after translation in all eukaryotic cells. While the N-terminal methionine on most proteins also is efficiently removed  
15 in most prokaryotes, for some proteins, this prokaryotic removal process is inefficient, depending on the nature of the amino acid to which the N-terminal methionine is covalently linked.

In one embodiment, the yeast *Pichia pastoris* is used to express polypeptides of the invention in a eukaryotic system. *Pichia pastoris* is a methylotrophic yeast  
20 which can metabolize methanol as its sole carbon source. A main step in the methanol metabolism pathway is the oxidation of methanol to formaldehyde using O<sub>2</sub>. This reaction is catalyzed by the enzyme alcohol oxidase. In order to metabolize methanol as its sole carbon source, *Pichia pastoris* must generate high levels of alcohol oxidase due, in part, to the relatively low affinity of alcohol oxidase for O<sub>2</sub>.  
25 Consequently, in a growth medium depending on methanol as a main carbon source, the promoter region of one of the two alcohol oxidase genes (*AOX1*) is highly active. In the presence of methanol, alcohol oxidase produced from the *AOX1* gene comprises up to approximately 30% of the total soluble protein in *Pichia pastoris*. See, Ellis, S.B., et al., *Mol. Cell. Biol.* 5:1111-21 (1985); Koutz, P.J., et al., *Yeast*

5:167-77 (1989); Tschopp, J.F., *et al.* *Nucl. Acids Res.* 15:3859-76 (1987). Thus, a heterologous coding sequence, such as, for example, a polynucleotide of the present invention, under the transcriptional regulation of all or part of the *AOX1* regulatory sequence is expressed at exceptionally high levels in *Pichia* yeast grown in the presence of methanol.

In one example, the plasmid vector pPIC9K is used to express DNA encoding a polypeptide of the invention, as set forth herein, in a *Pichea* yeast system essentially as described in "*Pichia* Protocols: Methods in Molecular Biology," D.R. Higgins and J. Cregg, eds. The Humana Press, Totowa, NJ, 1998. This expression vector allows expression and secretion of a polypeptide of the invention by virtue of the strong *AOX1* promoter linked to the *Pichia pastoris* alkaline phosphatase (PHO) secretory signal peptide (i.e., leader) located upstream of a multiple cloning site.

Many other yeast vectors could be used in place of pPIC9K, such as, pYES2, pYD1, pTEF1/Zeo, pYES2/GS, pPICZ, pGAPZ, pGAPZalpha, pPIC9, pPIC3.5, pHIL-D2, pHIL-S1, pPIC3.5K, and PAO815, as one skilled in the art would readily appreciate, as long as the proposed expression construct provides appropriately located signals for transcription, translation, secretion (if desired), and the like, including an in-frame AUG as required.

In another embodiment, high-level expression of a heterologous coding sequence, such as, for example, a polynucleotide of the present invention, may be achieved by cloning the heterologous polynucleotide of the invention into an expression vector such as, for example, pGAPZ or pGAPZalpha, and growing the yeast culture in the absence of methanol.

In addition to encompassing host cells containing the vector constructs discussed herein, the invention also encompasses primary, secondary, and immortalized host cells of vertebrate origin, particularly mammalian origin, that have been engineered to delete or replace endogenous genetic material (e.g., coding sequence), and/or to include genetic material (e.g., heterologous polynucleotide sequences) that is operably associated with polynucleotides of the invention, and

which activates, alters, and/or amplifies endogenous polynucleotides. For example, techniques known in the art may be used to operably associate heterologous control regions (e.g., promoter and/or enhancer) and endogenous polynucleotide sequences via homologous recombination (see, e.g., U.S. Patent No. 5,641,670, issued June 24, 1997; International Publication No. WO 96/29411, published September 26, 1996; International Publication No. WO 94/12650, published August 4, 1994; Koller et al., Proc. Natl. Acad. Sci. USA 86:8932-8935 (1989); and Zijlstra et al., Nature 342:435-438 (1989), the disclosures of each of which are incorporated by reference in their entireties).

10 In addition, polypeptides of the invention can be chemically synthesized using techniques known in the art (e.g., see Creighton, 1983, Proteins: Structures and Molecular Principles, W.H. Freeman & Co., N.Y., and Hunkapiller et al., *Nature*, 310:105-111 (1984)). For example, a polypeptide corresponding to a fragment of a polypeptide can be synthesized by use of a peptide synthesizer. Furthermore, if  
15 desired, nonclassical amino acids or chemical amino acid analogs can be introduced as a substitution or addition into the polypeptide sequence. Non-classical amino acids include, but are not limited to, to the D-isomers of the common amino acids, 2,4-diaminobutyric acid,  $\alpha$ -amino isobutyric acid, 4-aminobutyric acid, Abu, 2-amino butyric acid,  $\gamma$ -Abu,  $\epsilon$ -Ahx, 6-amino hexanoic acid, Aib, 2-amino isobutyric acid,  
20 3-amino propionic acid, ornithine, norleucine, norvaline, hydroxyproline, sarcosine, citrulline, homocitrulline, cysteic acid, t-butylglycine, t-butylalanine, phenylglycine, cyclohexylalanine,  $\beta$ -alanine, fluoro-amino acids, designer amino acids such as  $\beta$ -methyl amino acids, Ca-methyl amino acids, Na-methyl amino acids, and amino acid analogs in general. Furthermore, the amino acid can be D (dextrorotary) or L  
25 (levorotary).

Non-naturally occurring variants may be produced using art-known mutagenesis techniques, which include, but are not limited to oligonucleotide mediated mutagenesis, alanine scanning, PCR mutagenesis, site directed mutagenesis (see, e.g., Carter et al., *Nucl. Acids Res.* 13:4331 (1986); and Zoller et al., *Nucl. Acids Res.* 10:6487 (1982)), cassette mutagenesis (see, e.g., Wells et al., *Gene* 34:315  
30

(1985)), restriction selection mutagenesis (*see, e.g., Wells et al., Philos. Trans. R. Soc. London SerA 317:415 (1986)*).

The invention additionally, encompasses polypeptides of the present invention which are differentially modified during or after translation, e.g., by glycosylation, acetylation, phosphorylation, amidation, derivatization by known protecting/blocking groups, proteolytic cleavage, linkage to an antibody molecule or other cellular ligand, etc. Any of numerous chemical modifications may be carried out by known techniques, including but not limited, to specific chemical cleavage by cyanogen bromide, trypsin, chymotrypsin, papain, V8 protease, NaBH<sub>4</sub>; acetylation, formylation, oxidation, reduction; metabolic synthesis in the presence of tunicamycin; etc.

Additional post-translational modifications encompassed by the invention include, for example, e.g., N-linked or O-linked carbohydrate chains, processing of N-terminal or C-terminal ends), attachment of chemical moieties to the amino acid backbone, chemical modifications of N-linked or O-linked carbohydrate chains, and addition or deletion of an N-terminal methionine residue as a result of procaryotic host cell expression. The polypeptides may also be modified with a detectable label, such as an enzymatic, fluorescent, isotopic or affinity label to allow for detection and isolation of the protein.

Also provided by the invention are chemically modified derivatives of the polypeptides of the invention which may provide additional advantages such as increased solubility, stability and circulating time of the polypeptide, or decreased immunogenicity (*see U.S. Patent No. 4,179,337*). The chemical moieties for derivitization may be selected from water soluble polymers such as polyethylene glycol, ethylene glycol/propylene glycol copolymers, carboxymethylcellulose, dextran, polyvinyl alcohol and the like. The polypeptides may be modified at random positions within the molecule, or at predetermined positions within the molecule and may include one, two, three or more attached chemical moieties.

The polymer may be of any molecular weight, and may be branched or unbranched. For polyethylene glycol, the preferred molecular weight is between

about 1 kDa and about 100 kDa (the term "about" indicating that in preparations of polyethylene glycol, some molecules will weigh more, some less, than the stated molecular weight) for ease in handling and manufacturing. Other sizes may be used, depending on the desired therapeutic profile (e.g., the duration of sustained release  
5 desired, the effects, if any on biological activity, the ease in handling, the degree or lack of antigenicity and other known effects of the polyethylene glycol to a therapeutic protein or analog). For example, the polyethylene glycol may have an average molecular weight of about 200; 500; 1000; 1500; 2000; 2500; 3000; 3500; 4000; 4500; 5000; 5500; 6000; 6500; 7000; 7500; 8000; 8500; 9000; 9500; 10,000;  
10 10,500; 11,000; 11,500; 12,000; 12,500; 13,000; 13,500; 14,000; 14,500; 15,000; 15,500; 16,000; 16,500; 17,000; 17,500; 18,000; 18,500; 19,000; 19,500; 20,000; 25,000; 30,000; 35,000; 40,000; 50,000; 55,000; 60,000; 65,000; 70,000; 75,000; 80,000; 85,000; 90,000; 95,000; or 100,000 kDa.

As noted above, the polyethylene glycol may have a branched structure.  
15 Branched polyethylene glycols are described, for example, in U.S. Patent No. 5,643,575; Morpurgo *et al.*, *Appl. Biochem. Biotechnol.* 56:59-72 (1996); Vorobjev *et al.*, *Nucleosides Nucleotides* 18:2745-2750 (1999); and Caliceti *et al.*, *Bioconjug. Chem.* 10:638-646 (1999), the disclosures of each of which are incorporated herein by reference.

20 The polyethylene glycol molecules (or other chemical moieties) should be attached to the protein with consideration of effects on functional or antigenic domains of the protein. There are a number of attachment methods available to those skilled in the art, e.g., EP 0 401 384, herein incorporated by reference (coupling PEG to G-CSF), see also Malik *et al.*, *Exp. Hematol.* 20:1028-1035 (1992) (reporting  
25 pegylation of GM-CSF using tresyl chloride). For example, polyethylene glycol may be covalently bound through amino acid residues via a reactive group, such as, a free amino or carboxyl group. Reactive groups are those to which an activated polyethylene glycol molecule may be bound. The amino acid residues having a free amino group may include lysine residues and the N-terminal amino acid residues;  
30 those having a free carboxyl group may include aspartic acid residues glutamic acid



residues and the C-terminal amino acid residue. Sulfhydryl groups may also be used as a reactive group for attaching the polyethylene glycol molecules. Preferred for therapeutic purposes is attachment at an amino group, such as attachment at the N-terminus or lysine group.

5       As suggested above, polyethylene glycol may be attached to proteins via linkage to any of a number of amino acid residues. For example, polyethylene glycol can be linked to a proteins via covalent bonds to lysine, histidine, aspartic acid, glutamic acid, or cysteine residues. One or more reaction chemistries may be employed to attach polyethylene glycol to specific amino acid residues (e.g., lysine,  
10   histidine, aspartic acid, glutamic acid, or cysteine) of the protein or to more than one type of amino acid residue (e.g., lysine, histidine, aspartic acid, glutamic acid, cysteine and combinations thereof) of the protein.

One may specifically desire proteins chemically modified at the N-terminus. Using polyethylene glycol as an illustration of the present composition, one may  
15   select from a variety of polyethylene glycol molecules (by molecular weight, branching, etc.), the proportion of polyethylene glycol molecules to protein (polypeptide) molecules in the reaction mix, the type of pegylation reaction to be performed, and the method of obtaining the selected N-terminally pegylated protein. The method of obtaining the N-terminally pegylated preparation (i.e., separating this  
20   moiety from other monopegylated moieties if necessary) may be by purification of the N-terminally pegylated material from a population of pegylated protein molecules. Selective proteins chemically modified at the N-terminus modification may be accomplished by reductive alkylation which exploits differential reactivity of different types of primary amino groups (lysine versus the N-terminal) available for  
25   derivatization in a particular protein. Under the appropriate reaction conditions, substantially selective derivatization of the protein at the N-terminus with a carbonyl group containing polymer is achieved.

As indicated above, pegylation of the proteins of the invention may be accomplished by any number of means. For example, polyethylene glycol may be  
30   attached to the protein either directly or by an intervening linker. Linkerless systems

for attaching polyethylene glycol to proteins are described in Delgado *et al.*, *Crit. Rev. Thera. Drug Carrier Sys.* 9:249-304 (1992); Francis *et al.*, *Intern. J. of Hematol.* 68:1-18 (1998); U.S. Patent No. 4,002,531; U.S. Patent No. 5,349,052; WO 95/06058; and WO 98/32466, the disclosures of each of which are incorporated  
5 herein by reference.

One system for attaching polyethylene glycol directly to amino acid residues of proteins without an intervening linker employs tresylated MPEG, which is produced by the modification of monmethoxy polyethylene glycol (MPEG) using tresylchloride ( $\text{ClSO}_2\text{CH}_2\text{CF}_3$ ). Upon reaction of protein with tresylated MPEG,  
10 polyethylene glycol is directly attached to amine groups of the protein. Thus, the invention includes protein-polyethylene glycol conjugates produced by reacting proteins of the invention with a polyethylene glycol molecule having a 2,2,2-trifluoroethane sulphonyl group.

Polyethylene glycol can also be attached to proteins using a number of  
15 different intervening linkers. For example, U.S. Patent No. 5,612,460, the entire disclosure of which is incorporated herein by reference, discloses urethane linkers for connecting polyethylene glycol to proteins. Protein-polyethylene glycol conjugates wherein the polyethylene glycol is attached to the protein by a linker can also be produced by reaction of proteins with compounds such as MPEG-succinimidylsuccinate, MPEG activated with 1,1'-carbonyldiimidazole, MPEG-  
20 2,4,5-trichloropenylcarbonate, MPEG-p-nitrophenolcarbonate, and various MPEG-succinate derivatives. A number additional polyethylene glycol derivatives and reaction chemistries for attaching polyethylene glycol to proteins are described in WO 98/32466, the entire disclosure of which is incorporated herein by reference.  
25 Pegylated protein products produced using the reaction chemistries set out herein are included within the scope of the invention.

The number of polyethylene glycol moieties attached to each protein of the invention (*i.e.*, the degree of substitution) may also vary. For example, the pegylated proteins of the invention may be linked, on average, to 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12,  
30 15, 17, 20, or more polyethylene glycol molecules. Similarly, the average degree of

substitution within ranges such as 1-3, 2-4, 3-5, 4-6, 5-7, 6-8, 7-9, 8-10, 9-11, 10-12, 11-13, 12-14, 13-15, 14-16, 15-17, 16-18, 17-19, or 18-20 polyethylene glycol moieties per protein molecule. Methods for determining the degree of substitution are discussed, for example, in Delgado *et al.*, *Crit. Rev. Thera. Drug Carrier Sys.* 9:249-304 (1992).

The cancer antigen polypeptides of the invention may be in monomers or multimers (i.e., dimers, trimers, tetramers and higher multimers). Accordingly, the present invention relates to monomers and multimers of the polypeptides of the invention, their preparation, and compositions (preferably, Therapeutics) containing them. In specific embodiments, the polypeptides of the invention are monomers, dimers, trimers or tetramers. In additional embodiments, the multimers of the invention are at least dimers, at least trimers, or at least tetramers.

Multimers encompassed by the invention may be homomers or heteromers. As used herein, the term homomer, refers to a multimer containing only polypeptides corresponding to the amino acid sequence of SEQ ID NO:Y or an amino acid sequence encoded by SEQ ID NO:X, and/or an amino acid sequence encoded by the cDNA in a related cDNA clone contained in a deposited library (including fragments, variants, splice variants, and fusion proteins, corresponding to any one of these as described herein). These homomers may contain polypeptides having identical or different amino acid sequences. In a specific embodiment, a homomer of the invention is a multimer containing only polypeptides having an identical amino acid sequence. In another specific embodiment, a homomer of the invention is a multimer containing polypeptides having different amino acid sequences. In specific embodiments, the multimer of the invention is a homodimer (e.g., containing polypeptides having identical or different amino acid sequences) or a homotrimer (e.g., containing polypeptides having identical and/or different amino acid sequences). In additional embodiments, the homomeric multimer of the invention is at least a homodimer, at least a homotrimer, or at least a homotetramer.

As used herein, the term heteromer refers to a multimer containing one or more heterologous polypeptides (i.e., polypeptides of different proteins) in addition to

the polypeptides of the invention. In a specific embodiment, the multimer of the invention is a heterodimer, a heterotrimer, or a heterotetramer. In additional embodiments, the heteromeric multimer of the invention is at least a heterodimer, at least a heterotrimer, or at least a heterotetramer.

5           Multimers of the invention may be the result of hydrophobic, hydrophilic, ionic and/or covalent associations and/or may be indirectly linked, by for example, liposome formation. Thus, in one embodiment, multimers of the invention, such as, for example, homodimers or homotrimers, are formed when polypeptides of the invention contact one another in solution. In another embodiment, heteromultimers  
10 of the invention, such as, for example, heterotrimers or heterotetramers, are formed when polypeptides of the invention contact antibodies to the polypeptides of the invention (including antibodies to the heterologous polypeptide sequence in a fusion protein of the invention) in solution. In other embodiments, multimers of the invention are formed by covalent associations with and/or between the polypeptides  
15 of the invention. Such covalent associations may involve one or more amino acid residues contained in the polypeptide sequence (e.g., that recited in SEQ ID NO:Y, or contained in a polypeptide encoded by SEQ ID NO:X, and/or by the cDNA in the related cDNA clone contained in a deposited library). In one instance, the covalent associations are cross-linking between cysteine residues located within the  
20 polypeptide sequences which interact in the native (i.e., naturally occurring) polypeptide. In another instance, the covalent associations are the consequence of chemical or recombinant manipulation. Alternatively, such covalent associations may involve one or more amino acid residues contained in the heterologous polypeptide sequence in a fusion protein. In one example, covalent associations are between the  
25 heterologous sequence contained in a fusion protein of the invention (see, e.g., US Patent Number 5,478,925). In a specific example, the covalent associations are between the heterologous sequence contained in a Fc fusion protein of the invention (as described herein). In another specific example, covalent associations of fusion proteins of the invention are between heterologous polypeptide sequence from  
30 another protein that is capable of forming covalently associated multimers, such as for

example, osteoprotegerin (see, e.g., International Publication NO: WO 98/49305, the contents of which are herein incorporated by reference in its entirety). In another embodiment, two or more polypeptides of the invention are joined through peptide linkers. Examples include those peptide linkers described in U.S. Pat. No. 5,073,627 (hereby incorporated by reference). Proteins comprising multiple polypeptides of the invention separated by peptide linkers may be produced using conventional recombinant DNA technology.

Another method for preparing multimer polypeptides of the invention involves use of polypeptides of the invention fused to a leucine zipper or isoleucine zipper polypeptide sequence. Leucine zipper and isoleucine zipper domains are polypeptides that promote multimerization of the proteins in which they are found. Leucine zippers were originally identified in several DNA-binding proteins (Landschulz et al., Science 240:1759, (1988)), and have since been found in a variety of different proteins. Among the known leucine zippers are naturally occurring peptides and derivatives thereof that dimerize or trimerize. Examples of leucine zipper domains suitable for producing soluble multimeric proteins of the invention are those described in PCT application WO 94/10308, hereby incorporated by reference. Recombinant fusion proteins comprising a polypeptide of the invention fused to a polypeptide sequence that dimerizes or trimerizes in solution are expressed in suitable host cells, and the resulting soluble multimeric fusion protein is recovered from the culture supernatant using techniques known in the art.

Trimeric polypeptides of the invention may offer the advantage of enhanced biological activity. Preferred leucine zipper moieties and isoleucine moieties are those that preferentially form trimers. One example is a leucine zipper derived from lung surfactant protein D (SPD), as described in Hoppe et al. (FEBS Letters 344:191, (1994)) and in U.S. patent application Ser. No. 08/446,922, hereby incorporated by reference. Other peptides derived from naturally occurring trimeric proteins may be employed in preparing trimeric polypeptides of the invention.

In another example, proteins of the invention are associated by interactions between Flag® polypeptide sequence contained in fusion proteins of the invention

containing Flag® polypeptide sequence. In a further embodiment, associations proteins of the invention are associated by interactions between heterologous polypeptide sequence contained in Flag® fusion proteins of the invention and anti-Flag® antibody.

5           The multimers of the invention may be generated using chemical techniques known in the art. For example, polypeptides desired to be contained in the multimers of the invention may be chemically cross-linked using linker molecules and linker molecule length optimization techniques known in the art (see, e.g., US Patent Number 5,478,925, which is herein incorporated by reference in its entirety).  
10       Additionally, multimers of the invention may be generated using techniques known in the art to form one or more inter-molecule cross-links between the cysteine residues located within the sequence of the polypeptides desired to be contained in the multimer (see, e.g., US Patent Number 5,478,925, which is herein incorporated by reference in its entirety). Further, polypeptides of the invention may be routinely  
15       modified by the addition of cysteine or biotin to the C-terminus or N-terminus of the polypeptide and techniques known in the art may be applied to generate multimers containing one or more of these modified polypeptides (see, e.g., US Patent Number 5,478,925, which is herein incorporated by reference in its entirety). Additionally, techniques known in the art may be applied to generate liposomes containing the  
20       polypeptide components desired to be contained in the multimer of the invention (see, e.g., US Patent Number 5,478,925, which is herein incorporated by reference in its entirety).

          Alternatively, multimers of the invention may be generated using genetic engineering techniques known in the art. In one embodiment, polypeptides contained  
25       in multimers of the invention are produced recombinantly using fusion protein technology described herein or otherwise known in the art (see, e.g., US Patent Number 5,478,925, which is herein incorporated by reference in its entirety). In a specific embodiment, polynucleotides coding for a homodimer of the invention are generated by ligating a polynucleotide sequence encoding a polypeptide of the  
30       invention to a sequence encoding a linker polypeptide and then further to a synthetic

polynucleotide encoding the translated product of the polypeptide in the reverse orientation from the original C-terminus to the N-terminus (lacking the leader sequence) (see, e.g., US Patent Number 5,478,925, which is herein incorporated by reference in its entirety). In another embodiment, recombinant techniques described  
5 herein or otherwise known in the art are applied to generate recombinant polypeptides of the invention which contain a transmembrane domain (or hydrophobic or signal peptide) and which can be incorporated by membrane reconstitution techniques into liposomes (see, e.g., US Patent Number 5,478,925, which is herein incorporated by reference in its entirety).

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### **Antibodies**

Further polypeptides of the invention relate to antibodies and T-cell antigen receptors (TCR) which immunospecifically bind a polypeptide, polypeptide fragment, or variant of SEQ ID NO:Y, and/or an epitope, of the present invention (as  
15 determined by immunoassays well known in the art for assaying specific antibody-antigen binding). Antibodies of the invention include, but are not limited to, polyclonal, monoclonal, multispecific, human, humanized or chimeric antibodies, single chain antibodies, Fab fragments, F(ab') fragments, fragments produced by a Fab expression library, anti-idiotypic (anti-Id) antibodies (including, e.g., anti-Id  
20 antibodies to antibodies of the invention), and epitope-binding fragments of any of the above. The term "antibody," as used herein, refers to immunoglobulin molecules and immunologically active portions of immunoglobulin molecules, i.e., molecules that contain an antigen binding site that immunospecifically binds an antigen. The immunoglobulin molecules of the invention can be of any type (e.g., IgG, IgE, IgM,  
25 IgD, IgA and IgY), class (e.g., IgG1, IgG2, IgG3, IgG4, IgA1 and IgA2) or subclass of immunoglobulin molecule.

Most preferably the antibodies are human antigen-binding antibody fragments of the present invention and include, but are not limited to, Fab, Fab' and F(ab')<sub>2</sub>, Fd, single-chain Fvs (scFv), single-chain antibodies, disulfide-linked Fvs (sdFv) and  
30 fragments comprising either a VL or VH domain. Antigen-binding antibody

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fragments, including single-chain antibodies, may comprise the variable region(s) alone or in combination with the entirety or a portion of the following: hinge region; CH1, CH2, and CH3 domains. Also included in the invention are antigen-binding fragments also comprising any combination of variable region(s) with a hinge region, CH1, CH2, and CH3 domains. The antibodies of the invention may be from any animal origin including birds and mammals. Preferably, the antibodies are human, murine (e.g., mouse and rat), donkey, ship rabbit, goat, guinea pig, camel, horse, or chicken. As used herein, "human" antibodies include antibodies having the amino acid sequence of a human immunoglobulin and include antibodies isolated from human immunoglobulin libraries or from animals transgenic for one or more human immunoglobulin and that do not express endogenous immunoglobulins, as described infra and, for example in, U.S. Patent No. 5,939,598 by Kucherlapati et al.

The antibodies of the present invention may be monospecific, bispecific, trispecific or of greater multispecificity. Multispecific antibodies may be specific for different epitopes of a polypeptide of the present invention or may be specific for both a polypeptide of the present invention as well as for a heterologous epitope, such as a heterologous polypeptide or solid support material. See, e.g., PCT publications WO 93/17715; WO 92/08802; WO 91/00360; WO 92/05793; Tutt, et al., J. Immunol. 147:60-69 (1991); U.S. Patent Nos. 4,474,893; 4,714,681; 4,925,648; 5,573,920; 5,601,819; Kostelny et al., J. Immunol. 148:1547-1553 (1992).

Antibodies of the present invention may be described or specified in terms of the epitope(s) or portion(s) of a polypeptide of the present invention which they recognize or specifically bind. The epitope(s) or polypeptide portion(s) may be specified as described herein, e.g., by N-terminal and C-terminal positions, or by size in contiguous amino acid residues. Antibodies which specifically bind any epitope or polypeptide of the present invention may also be excluded. Therefore, the present invention includes antibodies that specifically bind polypeptides of the present invention, and allows for the exclusion of the same.

Antibodies of the present invention may also be described or specified in terms of their cross-reactivity. Antibodies that do not bind any other analog, ortholog,



or homolog of a polypeptide of the present invention are included. Antibodies that bind polypeptides with at least 95%, at least 90%, at least 85%, at least 80%, at least 75%, at least 70%, at least 65%, at least 60%, at least 55%, and at least 50% identity (as calculated using methods known in the art and described herein) to a polypeptide of the present invention are also included in the present invention. In specific embodiments, antibodies of the present invention cross-react with murine, rat and/or rabbit homologs of human proteins and the corresponding epitopes thereof. Antibodies that do not bind polypeptides with less than 95%, less than 90%, less than 85%, less than 80%, less than 75%, less than 70%, less than 65%, less than 60%, less than 55%, and less than 50% identity (as calculated using methods known in the art and described herein) to a polypeptide of the present invention are also included in the present invention. In a specific embodiment, the above-described cross-reactivity is with respect to any single specific antigenic or immunogenic polypeptide, or combination(s) of 2, 3, 4, 5, or more of the specific antigenic and/or immunogenic polypeptides disclosed herein. Further included in the present invention are antibodies which bind polypeptides encoded by polynucleotides which hybridize to a polynucleotide of the present invention under stringent hybridization conditions (as described herein). Antibodies of the present invention may also be described or specified in terms of their binding affinity to a polypeptide of the invention. Preferred binding affinities include those with a dissociation constant or  $K_d$  less than  $5 \times 10^{-2}$  M,  $10^{-2}$  M,  $5 \times 10^{-3}$  M,  $10^{-3}$  M,  $5 \times 10^{-4}$  M,  $10^{-4}$  M,  $5 \times 10^{-5}$  M,  $10^{-5}$  M,  $5 \times 10^{-6}$  M,  $10^{-6}$  M,  $5 \times 10^{-7}$  M,  $10^{-7}$  M,  $5 \times 10^{-8}$  M,  $10^{-8}$  M,  $5 \times 10^{-9}$  M,  $10^{-9}$  M,  $5 \times 10^{-10}$  M,  $10^{-10}$  M,  $5 \times 10^{-11}$  M,  $10^{-11}$  M,  $5 \times 10^{-12}$  M,  $10^{-12}$  M,  $5 \times 10^{-13}$  M,  $10^{-13}$  M,  $5 \times 10^{-14}$  M,  $10^{-14}$  M,  $5 \times 10^{-15}$  M, or  $10^{-15}$  M.

The invention also provides antibodies that competitively inhibit binding of an antibody to an epitope of the invention as determined by any method known in the art for determining competitive binding, for example, the immunoassays described herein. In preferred embodiments, the antibody competitively inhibits binding to the epitope by at least 95%, at least 90%, at least 85 %, at least 80%, at least 75%, at least 70%, at least 60%, or at least 50%.

Antibodies of the present invention may act as agonists or antagonists of the polypeptides of the present invention. For example, the present invention includes antibodies which disrupt the receptor/ligand interactions with the polypeptides of the invention either partially or fully. Preferably, antibodies of the present invention  
5 bind an antigenic epitope disclosed herein, or a portion thereof. The invention features both receptor-specific antibodies and ligand-specific antibodies. The invention also features receptor-specific antibodies which do not prevent ligand binding but prevent receptor activation. Receptor activation (i.e., signaling) may be determined by techniques described herein or otherwise known in the art. For example, receptor  
10 activation can be determined by detecting the phosphorylation (e.g., tyrosine or serine/threonine) of the receptor or its substrate by immunoprecipitation followed by western blot analysis (for example, as described supra). In specific embodiments, antibodies are provided that inhibit ligand activity or receptor activity by at least 95%, at least 90%, at least 85%, at least 80%, at least 75%, at least 70%, at least 60%, or at  
15 least 50% of the activity in absence of the antibody.

The invention also features receptor-specific antibodies which both prevent ligand binding and receptor activation as well as antibodies that recognize the receptor-ligand complex, and, preferably, do not specifically recognize the unbound receptor or the unbound ligand. Likewise, included in the invention are neutralizing  
20 antibodies which bind the ligand and prevent binding of the ligand to the receptor, as well as antibodies which bind the ligand, thereby preventing receptor activation, but do not prevent the ligand from binding the receptor. Further included in the invention are antibodies which activate the receptor. These antibodies may act as receptor agonists, i.e., potentiate or activate either all or a subset of the biological activities of  
25 the ligand-mediated receptor activation, for example, by inducing dimerization of the receptor. The antibodies may be specified as agonists, antagonists or inverse agonists for biological activities comprising the specific biological activities of the peptides of the invention disclosed herein. The above antibody agonists can be made using methods known in the art. See, e.g., PCT publication WO 96/40281; U.S. Patent No.  
30 5,811,097; Deng et al., Blood 92(6):1981-1988 (1998); Chen et al., Cancer Res.

58(16):3668-3678 (1998); Harrop et al., *J. Immunol.* 161(4):1786-1794 (1998); Zhu et al., *Cancer Res.* 58(15):3209-3214 (1998); Yoon et al., *J. Immunol.* 160(7):3170-3179 (1998); Prat et al., *J. Cell. Sci.* 111(Pt2):237-247 (1998); Pitard et al., *J. Immunol. Methods* 205(2):177-190 (1997); Liautard et al., *Cytokine* 9(4):233-241 (1997); Carlson et al., *J. Biol. Chem.* 272(17):11295-11301 (1997); Taryman et al., *Neuron* 14(4):755-762 (1995); Muller et al., *Structure* 6(9):1153-1167 (1998); Bartunek et al., *Cytokine* 8(1):14-20 (1996) (which are all incorporated by reference herein in their entireties).

Antibodies of the present invention may be used, for example, but not limited to, to purify, detect, and target the polypeptides of the present invention, including both in vitro and in vivo diagnostic and therapeutic methods. For example, the antibodies have use in immunoassays for qualitatively and quantitatively measuring levels of the polypeptides of the present invention in biological samples. See, e.g., Harlow et al., *Antibodies: A Laboratory Manual*, (Cold Spring Harbor Laboratory Press, 2nd ed. 1988) (incorporated by reference herein in its entirety).

As discussed in more detail below, the antibodies of the present invention may be used either alone or in combination with other compositions. The antibodies may further be recombinantly fused to a heterologous polypeptide at the N- or C-terminus or chemically conjugated (including covalently and non-covalently conjugations) to polypeptides or other compositions. For example, antibodies of the present invention may be recombinantly fused or conjugated to molecules useful as labels in detection assays and effector molecules such as heterologous polypeptides, drugs, radionuclides, or toxins. See, e.g., PCT publications WO 92/08495; WO 91/14438; WO 89/12624; U.S. Patent No. 5,314,995; and EP 396,387.

The antibodies of the invention include derivatives that are modified, i.e., by the covalent attachment of any type of molecule to the antibody such that covalent attachment does not prevent the antibody from generating an anti-idiotypic response. For example, but not by way of limitation, the antibody derivatives include antibodies that have been modified, e.g., by glycosylation, acetylation, pegylation, phosphorylation, amidation, derivatization by known protecting/blocking groups,

proteolytic cleavage, linkage to a cellular ligand or other protein, etc. Any of numerous chemical modifications may be carried out by known techniques, including, but not limited to specific chemical cleavage, acetylation, formylation, metabolic synthesis of tunicamycin, etc. Additionally, the derivative may contain one or more  
5 non-classical amino acids.

The antibodies of the present invention may be generated by any suitable method known in the art. Polyclonal antibodies to an antigen-of- interest can be produced by various procedures well known in the art. For example, a polypeptide of the invention can be administered to various host animals including, but not limited  
10 to, rabbits, mice, rats, etc. to induce the production of sera containing polyclonal antibodies specific for the antigen. Various adjuvants may be used to increase the immunological response, depending on the host species, and include but are not limited to, Freund's (complete and incomplete), mineral gels such as aluminum hydroxide, surface active substances such as lysolecithin, pluronic polyols,  
15 polyanions, peptides, oil emulsions, keyhole limpet hemocyanins, dinitrophenol, and potentially useful human adjuvants such as BCG (bacille Calmette-Guerin) and corynebacterium parvum. Such adjuvants are also well known in the art.

Monoclonal antibodies can be prepared using a wide variety of techniques known in the art including the use of hybridoma, recombinant, and phage display  
20 technologies, or a combination thereof. For example, monoclonal antibodies can be produced using hybridoma techniques including those known in the art and taught, for example, in Harlow et al., *Antibodies: A Laboratory Manual*, (Cold Spring Harbor Laboratory Press, 2nd ed. 1988); Hammerling, et al., in: *Monoclonal Antibodies and T-Cell Hybridomas* 563-681 (Elsevier, N.Y., 1981) (said references incorporated by  
25 reference in their entirety). The term "monoclonal antibody" as used herein is not limited to antibodies produced through hybridoma technology. The term "monoclonal antibody" refers to an antibody that is derived from a single clone, including any eukaryotic, prokaryotic, or phage clone, and not the method by which it is produced.

Methods for producing and screening for specific antibodies using hybridoma technology are routine and well known in the art and are discussed in detail in the Examples. In a non-limiting example, mice can be immunized with a polypeptide of the invention or a cell expressing such peptide. Once an immune response is detected, e.g., antibodies specific for the antigen are detected in the mouse serum, the mouse spleen is harvested and splenocytes isolated. The splenocytes are then fused by well known techniques to any suitable myeloma cells, for example cells from cell line SP20 available from the ATCC. Hybridomas are selected and cloned by limited dilution. The hybridoma clones are then assayed by methods known in the art for cells that secrete antibodies capable of binding a polypeptide of the invention. Ascites fluid, which generally contains high levels of antibodies, can be generated by immunizing mice with positive hybridoma clones.

Accordingly, the present invention provides methods of generating monoclonal antibodies as well as antibodies produced by the method comprising culturing a hybridoma cell secreting an antibody of the invention wherein, preferably, the hybridoma is generated by fusing splenocytes isolated from a mouse immunized with an antigen of the invention with myeloma cells and then screening the hybridomas resulting from the fusion for hybridoma clones that secrete an antibody able to bind a polypeptide of the invention.

Antibody fragments which recognize specific epitopes may be generated by known techniques. For example, Fab and F(ab')<sub>2</sub> fragments of the invention may be produced by proteolytic cleavage of immunoglobulin molecules, using enzymes such as papain (to produce Fab fragments) or pepsin (to produce F(ab')<sub>2</sub> fragments). F(ab')<sub>2</sub> fragments contain the variable region, the light chain constant region and the CH1 domain of the heavy chain.

For example, the antibodies of the present invention can also be generated using various phage display methods known in the art. In phage display methods, functional antibody domains are displayed on the surface of phage particles which carry the polynucleotide sequences encoding them. In a particular embodiment, such phage can be utilized to display antigen binding domains expressed from a repertoire

or combinatorial antibody library (e.g., human or murine). Phage expressing an antigen binding domain that binds the antigen of interest can be selected or identified with antigen, e.g., using labeled antigen or antigen bound or captured to a solid surface or bead. Phage used in these methods are typically filamentous phage including fd and M13 binding domains expressed from phage with Fab, Fv or disulfide stabilized Fv antibody domains recombinantly fused to either the phage gene III or gene VIII protein. Examples of phage display methods that can be used to make the antibodies of the present invention include those disclosed in Brinkman et al., *J. Immunol. Methods* 182:41-50 (1995); Ames et al., *J. Immunol. Methods* 184:177-186 (1995); Kettleborough et al., *Eur. J. Immunol.* 24:952-958 (1994); Persic et al., *Gene* 187 9-18 (1997); Burton et al., *Advances in Immunology* 57:191-280 (1994); PCT application No. PCT/GB91/01134; PCT publications WO 90/02809; WO 91/10737; WO 92/01047; WO 92/18619; WO 93/11236; WO 95/15982; WO 95/20401; and U.S. Patent Nos. 5,698,426; 5,223,409; 5,403,484; 5,580,717; 5,427,908; 5,750,753; 5,821,047; 5,571,698; 5,427,908; 5,516,637; 5,780,225; 5,658,727; 5,733,743 and 5,969,108; each of which is incorporated herein by reference in its entirety.

As described in the above references, after phage selection, the antibody coding regions from the phage can be isolated and used to generate whole antibodies, including human antibodies, or any other desired antigen binding fragment, and expressed in any desired host, including mammalian cells, insect cells, plant cells, yeast, and bacteria, e.g., as described in detail below. For example, techniques to recombinantly produce Fab, Fab' and F(ab')<sub>2</sub> fragments can also be employed using methods known in the art such as those disclosed in PCT publication WO 92/22324; Mullinax et al., *BioTechniques* 12(6):864-869 (1992); and Sawai et al., *AJRI* 34:26-34 (1995); and Better et al., *Science* 240:1041-1043 (1988) (said references incorporated by reference in their entireties).

Examples of techniques which can be used to produce single-chain Fvs and antibodies include those described in U.S. Patents 4,946,778 and 5,258,498; Huston et al., *Methods in Enzymology* 203:46-88 (1991); Shu et al., *PNAS* 90:7995-7999

(1993); and Skerra et al., Science 240:1038-1040 (1988). For some uses, including in vivo use of antibodies in humans and in vitro detection assays, it may be preferable to use chimeric, humanized, or human antibodies. A chimeric antibody is a molecule in which different portions of the antibody are derived from different animal species, such as antibodies having a variable region derived from a murine monoclonal antibody and a human immunoglobulin constant region. Methods for producing chimeric antibodies are known in the art. See e.g., Morrison, Science 229:1202 (1985); Oi et al., BioTechniques 4:214 (1986); Gillies et al., (1989) J. Immunol. Methods 125:191-202; U.S. Patent Nos. 5,807,715; 4,816,567; and 4,816,397, which are incorporated herein by reference in their entirety. Humanized antibodies are antibody molecules from non-human species antibody that binds the desired antigen having one or more complementarity determining regions (CDRs) from the non-human species and a framework regions from a human immunoglobulin molecule. Often, framework residues in the human framework regions will be substituted with the corresponding residue from the CDR donor antibody to alter, preferably improve, antigen binding. These framework substitutions are identified by methods well known in the art, e.g., by modeling of the interactions of the CDR and framework residues to identify framework residues important for antigen binding and sequence comparison to identify unusual framework residues at particular positions. (See, e.g., Queen et al., U.S. Patent No. 5,585,089; Riechmann et al., Nature 332:323 (1988), which are incorporated herein by reference in their entirety.) Antibodies can be humanized using a variety of techniques known in the art including, for example, CDR-grafting (EP 239,400; PCT publication WO 91/09967; U.S. Patent Nos. 5,225,539; 5,530,101; and 5,585,089), veneering or resurfacing (EP 592,106; EP 519,596; Padlan, Molecular Immunology 28(4/5):489-498 (1991); Studnicka et al., Protein Engineering 7(6):805-814 (1994); Roguska. et al., PNAS 91:969-973 (1994)), and chain shuffling (U.S. Patent No. 5,565,332).

Completely human antibodies are particularly desirable for therapeutic treatment of human patients. Human antibodies can be made by a variety of methods known in the art including phage display methods described above using antibody

libraries derived from human immunoglobulin sequences. See also, U.S. Patent Nos. 4,444,887 and 4,716,111; and PCT publications WO 98/46645, WO 98/50433, WO 98/24893, WO 98/16654, WO 96/34096, WO 96/33735, and WO 91/10741; each of which is incorporated herein by reference in its entirety.

- 5 Human antibodies can also be produced using transgenic mice which are incapable of expressing functional endogenous immunoglobulins, but which can express human immunoglobulin genes. For example, the human heavy and light chain immunoglobulin gene complexes may be introduced randomly or by homologous recombination into mouse embryonic stem cells. Alternatively, the
- 10 human variable region, constant region, and diversity region may be introduced into mouse embryonic stem cells in addition to the human heavy and light chain genes. The mouse heavy and light chain immunoglobulin genes may be rendered non-functional separately or simultaneously with the introduction of human immunoglobulin loci by homologous recombination. In particular, homozygous
- 15 deletion of the *JH* region prevents endogenous antibody production. The modified embryonic stem cells are expanded and microinjected into blastocysts to produce chimeric mice. The chimeric mice are then bred to produce homozygous offspring which express human antibodies. The transgenic mice are immunized in the normal fashion with a selected antigen, e.g., all or a portion of a polypeptide of the invention.
- 20 Monoclonal antibodies directed against the antigen can be obtained from the immunized, transgenic mice using conventional hybridoma technology. The human immunoglobulin transgenes harbored by the transgenic mice rearrange during B cell differentiation, and subsequently undergo class switching and somatic mutation. Thus, using such a technique, it is possible to produce therapeutically useful IgG,
- 25 IgA, IgM and IgE antibodies. For an overview of this technology for producing human antibodies, see Lonberg and Huszar, *Int. Rev. Immunol.* 13:65-93 (1995). For a detailed discussion of this technology for producing human antibodies and human monoclonal antibodies and protocols for producing such antibodies, see, e.g., PCT publications WO 98/24893; WO 92/01047; WO 96/34096; WO 96/33735; European
- 30 Patent No. 0 598 877; U.S. Patent Nos. 5,413,923; 5,625,126; 5,633,425; 5,569,825;



5,661,016; 5,545,806; 5,814,318; 5,885,793; 5,916,771; and 5,939,598, which are incorporated by reference herein in their entirety. In addition, companies such as Abgenix, Inc. (Freemont, CA) and Genpharm (San Jose, CA) can be engaged to provide human antibodies directed against a selected antigen using technology similar to that described above.

Completely human antibodies which recognize a selected epitope can be generated using a technique referred to as "guided selection." In this approach a selected non-human monoclonal antibody, e.g., a mouse antibody, is used to guide the selection of a completely human antibody recognizing the same epitope. (Jespersen et al., Bio/technology 12:899-903 (1988)).

Further, antibodies to the polypeptides of the invention can, in turn, be utilized to generate anti-idiotypic antibodies that "mimic" polypeptides of the invention using techniques well known to those skilled in the art. (See, e.g., Greenspan & Bona, FASEB J. 7(5):437-444; (1989) and Nissinoff, J. Immunol. 147(8):2429-2438 (1991)). For example, antibodies which bind to and competitively inhibit polypeptide multimerization and/or binding of a polypeptide of the invention to a ligand can be used to generate anti-idiotypes that "mimic" the polypeptide multimerization and/or binding domain and, as a consequence, bind to and neutralize polypeptide and/or its ligand. Such neutralizing anti-idiotypes or Fab fragments of such anti-idiotypes can be used in therapeutic regimens to neutralize polypeptide ligand. For example, such anti-idiotypic antibodies can be used to bind a polypeptide of the invention and/or to bind its ligands/receptors, and thereby block its biological activity.

#### ***Polynucleotides Encoding Antibodies***

The invention further provides polynucleotides comprising a nucleotide sequence encoding an antibody of the invention and fragments thereof. The invention also encompasses polynucleotides that hybridize under stringent or alternatively, under lower stringency hybridization conditions, e.g., as defined supra, to polynucleotides that encode an antibody, preferably, that specifically binds to a

polypeptide of the invention, preferably, an antibody that binds to a polypeptide having the amino acid sequence of SEQ ID NO:Y.

The polynucleotides may be obtained, and the nucleotide sequence of the polynucleotides determined, by any method known in the art. For example, if the  
5 nucleotide sequence of the antibody is known, a polynucleotide encoding the antibody may be assembled from chemically synthesized oligonucleotides (e.g., as described in Kutmeier et al., *BioTechniques* 17:242 (1994)), which, briefly, involves the synthesis of overlapping oligonucleotides containing portions of the sequence encoding the antibody, annealing and ligating of those oligonucleotides, and then amplification of  
10 the ligated oligonucleotides by PCR.

Alternatively, a polynucleotide encoding an antibody may be generated from nucleic acid from a suitable source. If a clone containing a nucleic acid encoding a particular antibody is not available, but the sequence of the antibody molecule is known, a nucleic acid encoding the immunoglobulin may be chemically synthesized  
15 or obtained from a suitable source (e.g., an antibody cDNA library, or a cDNA library generated from, or nucleic acid, preferably poly A+ RNA, isolated from, any tissue or cells expressing the antibody, such as hybridoma cells selected to express an antibody of the invention) by PCR amplification using synthetic primers hybridizable to the 3' and 5' ends of the sequence or by cloning using an oligonucleotide probe  
20 specific for the particular gene sequence to identify, e.g., a cDNA clone from a cDNA library that encodes the antibody. Amplified nucleic acids generated by PCR may then be cloned into replicable cloning vectors using any method well known in the art.

Once the nucleotide sequence and corresponding amino acid sequence of the  
25 antibody is determined, the nucleotide sequence of the antibody may be manipulated using methods well known in the art for the manipulation of nucleotide sequences, e.g., recombinant DNA techniques, site directed mutagenesis, PCR, etc. (see, for example, the techniques described in Sambrook et al., 1990, *Molecular Cloning, A Laboratory Manual*, 2d Ed., Cold Spring Harbor Laboratory, Cold Spring Harbor, NY  
30 and Ausubel et al., eds., 1998, *Current Protocols in Molecular Biology*, John Wiley &

Sons, NY, which are both incorporated by reference herein in their entireties ), to generate antibodies having a different amino acid sequence. for example to create amino acid substitutions, deletions, and/or insertions.

In a specific embodiment, the amino acid sequence of the heavy and/or light  
5 chain variable domains may be inspected to identify the sequences of the complementarity determining regions (CDRs) by methods that are well know in the art, e.g., by comparison to known amino acid sequences of other heavy and light chain variable regions to determine the regions of sequence hypervariability. Using routine recombinant DNA techniques, one or more of the CDRs may be inserted  
10 within framework regions, e.g., into human framework regions to humanize a non-human antibody, as described supra. The framework regions may be naturally occurring or consensus framework regions, and preferably human framework regions (see, e.g., Chothia et al., J. Mol. Biol. 278: 457-479 (1998) for a listing of human framework regions). Preferably, the polynucleotide generated by the combination of  
15 the framework regions and CDRs encodes an antibody that specifically binds a polypeptide of the invention. Preferably, as discussed supra, one or more amino acid substitutions may be made within the framework regions, and, preferably, the amino acid substitutions improve binding of the antibody to its antigen. Additionally, such methods may be used to make amino acid substitutions or deletions of one or more  
20 variable region cysteine residues participating in an intrachain disulfide bond to generate antibody molecules lacking one or more intrachain disulfide bonds. Other alterations to the polynucleotide are encompassed by the present invention and within the skill of the art.

In addition, techniques developed for the production of "chimeric antibodies"  
25 (Morrison et al., Proc. Natl. Acad. Sci. 81:851-855 (1984); Neuberger et al., Nature 312:604-608 (1984); Takeda et al., Nature 314:452-454 (1985)) by splicing genes from a mouse antibody molecule of appropriate antigen specificity together with genes from a human antibody molecule of appropriate biological activity can be used. As described supra, a chimeric antibody is a molecule in which different portions are  
30 derived from different animal species, such as those having a variable region derived

from a murine mAb and a human immunoglobulin constant region, e.g., humanized antibodies.

Alternatively, techniques described for the production of single chain antibodies (U.S. Patent No. 4,946,778; Bird, Science 242:423- 42 (1988); Huston et al., Proc. Natl. Acad. Sci. USA 85:5879-5883 (1988); and Ward et al., Nature 334:544-54 (1989)) can be adapted to produce single chain antibodies. Single chain antibodies are formed by linking the heavy and light chain fragments of the Fv region via an amino acid bridge, resulting in a single chain polypeptide. Techniques for the assembly of functional Fv fragments in *E. coli* may also be used (Skerra et al., Science 242:1038- 1041 (1988)).

#### ***Methods of Producing Antibodies***

The antibodies of the invention can be produced by any method known in the art for the synthesis of antibodies, in particular, by chemical synthesis or preferably, by recombinant expression techniques.

Recombinant expression of an antibody of the invention, or fragment, derivative or analog thereof, (e.g., a heavy or light chain of an antibody of the invention or a single chain antibody of the invention), requires construction of an expression vector containing a polynucleotide that encodes the antibody. Once a polynucleotide encoding an antibody molecule or a heavy or light chain of an antibody, or portion thereof (preferably containing the heavy or light chain variable domain), of the invention has been obtained, the vector for the production of the antibody molecule may be produced by recombinant DNA technology using techniques well known in the art. Thus, methods for preparing a protein by expressing a polynucleotide containing an antibody encoding nucleotide sequence are described herein. Methods which are well known to those skilled in the art can be used to construct expression vectors containing antibody coding sequences and appropriate transcriptional and translational control signals. These methods include, for example, in vitro recombinant DNA techniques, synthetic techniques, and in vivo genetic recombination. The invention, thus, provides replicable vectors comprising a

nucleotide sequence encoding an antibody molecule of the invention, or a heavy or light chain thereof, or a heavy or light chain variable domain, operably linked to a promoter. Such vectors may include the nucleotide sequence encoding the constant region of the antibody molecule (see, e.g., PCT Publication WO 86/05807; PCT  
5 Publication WO 89/01036; and U.S. Patent No. 5,122,464) and the variable domain of the antibody may be cloned into such a vector for expression of the entire heavy or light chain.

The expression vector is transferred to a host cell by conventional techniques and the transfected cells are then cultured by conventional techniques to produce an  
10 antibody of the invention. Thus, the invention includes host cells containing a polynucleotide encoding an antibody of the invention, or a heavy or light chain thereof, or a single chain antibody of the invention, operably linked to a heterologous promoter. In preferred embodiments for the expression of double-chained antibodies, vectors encoding both the heavy and light chains may be co-expressed in the host cell  
15 for expression of the entire immunoglobulin molecule, as detailed below.

A variety of host-expression vector systems may be utilized to express the antibody molecules of the invention. Such host-expression systems represent vehicles by which the coding sequences of interest may be produced and subsequently purified, but also represent cells which may, when transformed or transfected with  
20 the appropriate nucleotide coding sequences, express an antibody molecule of the invention in situ. These include but are not limited to microorganisms such as bacteria (e.g., *E. coli*, *B. subtilis*) transformed with recombinant bacteriophage DNA, plasmid DNA or cosmid DNA expression vectors containing antibody coding sequences; yeast (e.g., *Saccharomyces*, *Pichia*) transformed with recombinant yeast  
25 expression vectors containing antibody coding sequences; insect cell systems infected with recombinant virus expression vectors (e.g., baculovirus) containing antibody coding sequences; plant cell systems infected with recombinant virus expression vectors (e.g., cauliflower mosaic virus, CaMV; tobacco mosaic virus, TMV) or transformed with recombinant plasmid expression vectors (e.g., Ti plasmid)  
30 containing antibody coding sequences; or mammalian cell systems (e.g., COS, CHO,

BHK, 293, 3T3 cells) harboring recombinant expression constructs containing promoters derived from the genome of mammalian cells (e.g., metallothionein promoter) or from mammalian viruses (e.g., the adenovirus late promoter; the vaccinia virus 7.5K promoter). Preferably, bacterial cells such as *Escherichia coli*,  
5 and more preferably, eukaryotic cells, especially for the expression of whole recombinant antibody molecule, are used for the expression of a recombinant antibody molecule. For example, mammalian cells such as Chinese hamster ovary cells (CHO), in conjunction with a vector such as the major intermediate early gene promoter element from human cytomegalovirus is an effective expression system for  
10 antibodies (Foecking et al., *Gene* 45:101 (1986); Cockett et al., *Bio/Technology* 8:2 (1990)).

In bacterial systems, a number of expression vectors may be advantageously selected depending upon the use intended for the antibody molecule being expressed. For example, when a large quantity of such a protein is to be produced, for the  
15 generation of pharmaceutical compositions of an antibody molecule, vectors which direct the expression of high levels of fusion protein products that are readily purified may be desirable. Such vectors include, but are not limited, to the *E. coli* expression vector pUR278 (Ruther et al., *EMBO J.* 2:1791 (1983)), in which the antibody coding sequence may be ligated individually into the vector in frame with the lac Z coding  
20 region so that a fusion protein is produced; pIN vectors (Inouye & Inouye, *Nucleic Acids Res.* 13:3101-3109 (1985); Van Heeke & Schuster, *J. Biol. Chem.* 24:5503-5509 (1989)); and the like. pGEX vectors may also be used to express foreign polypeptides as fusion proteins with glutathione S-transferase (GST). In general, such fusion proteins are soluble and can easily be purified from lysed cells by  
25 adsorption and binding to matrix glutathione-agarose beads followed by elution in the presence of free glutathione. The pGEX vectors are designed to include thrombin or factor Xa protease cleavage sites so that the cloned target gene product can be released from the GST moiety.

In an insect system, *Autographa californica* nuclear polyhedrosis virus  
30 (AcNPV) is used as a vector to express foreign genes. The virus grows in

*Spodoptera frugiperda* cells. The antibody coding sequence may be cloned individually into non-essential regions (for example the polyhedrin gene) of the virus and placed under control of an AcNPV promoter (for example the polyhedrin promoter).

5 In mammalian host cells, a number of viral-based expression systems may be utilized. In cases where an adenovirus is used as an expression vector, the antibody coding sequence of interest may be ligated to an adenovirus transcription/translation control complex, e.g., the late promoter and tripartite leader sequence. This chimeric gene may then be inserted in the adenovirus genome by in vitro or in vivo  
10 recombination. Insertion in a non-essential region of the viral genome (e.g., region E1 or E3) will result in a recombinant virus that is viable and capable of expressing the antibody molecule in infected hosts. (e.g., see Logan & Shenk, Proc. Natl. Acad. Sci. USA 81:355-359 (1984)). Specific initiation signals may also be required for efficient translation of inserted antibody coding sequences. These signals include the  
15 ATG initiation codon and adjacent sequences. Furthermore, the initiation codon must be in phase with the reading frame of the desired coding sequence to ensure translation of the entire insert. These exogenous translational control signals and initiation codons can be of a variety of origins, both natural and synthetic. The efficiency of expression may be enhanced by the inclusion of appropriate  
20 transcription enhancer elements, transcription terminators, etc. (see Bittner et al., Methods in Enzymol. 153:51-544 (1987)).

In addition, a host cell strain may be chosen which modulates the expression of the inserted sequences, or modifies and processes the gene product in the specific fashion desired. Such modifications (e.g., glycosylation) and processing (e.g.,  
25 cleavage) of protein products may be important for the function of the protein. Different host cells have characteristic and specific mechanisms for the post-translational processing and modification of proteins and gene products. Appropriate cell lines or host systems can be chosen to ensure the correct modification and processing of the foreign protein expressed. To this end, eukaryotic host cells which  
30 possess the cellular machinery for proper processing of the primary transcript,

glycosylation, and phosphorylation of the gene product may be used. Such mammalian host cells include but are not limited to CHO, VERO, BHK, HeLa, COS, MDCK, 293, 3T3, WI38, and in particular, breast cancer cell lines such as, for example, BT483, Hs578T, HTB2, BT20 and T47D, and normal mammary gland cell line such as, for example, CRL7030 and Hs578Bst.

For long-term, high-yield production of recombinant proteins, stable expression is preferred. For example, cell lines which stably express the antibody molecule may be engineered. Rather than using expression vectors which contain viral origins of replication, host cells can be transformed with DNA controlled by appropriate expression control elements (e.g., promoter, enhancer, sequences, transcription terminators, polyadenylation sites, etc.), and a selectable marker. Following the introduction of the foreign DNA, engineered cells may be allowed to grow for 1-2 days in an enriched media, and then are switched to a selective media. The selectable marker in the recombinant plasmid confers resistance to the selection and allows cells to stably integrate the plasmid into their chromosomes and grow to form foci which in turn can be cloned and expanded into cell lines. This method may advantageously be used to engineer cell lines which express the antibody molecule. Such engineered cell lines may be particularly useful in screening and evaluation of compounds that interact directly or indirectly with the antibody molecule.

A number of selection systems may be used, including but not limited to the herpes simplex virus thymidine kinase (Wigler et al., Cell 11:223 (1977)), hypoxanthine-guanine phosphoribosyltransferase (Szybalska & Szybalski, Proc. Natl. Acad. Sci. USA 48:202 (1992)), and adenine phosphoribosyltransferase (Lowy et al., Cell 22:817 (1980)) genes can be employed in tk-, hgpvt- or apvt- cells, respectively. Also, antimetabolite resistance can be used as the basis of selection for the following genes: dhfr, which confers resistance to methotrexate (Wigler et al., Natl. Acad. Sci. USA 77:357 (1980); O'Hare et al., Proc. Natl. Acad. Sci. USA 78:1527 (1981)); gpt, which confers resistance to mycophenolic acid (Mulligan & Berg, Proc. Natl. Acad. Sci. USA 78:2072 (1981)); neo, which confers resistance to the aminoglycoside G-418 Clinical Pharmacy 12:488-505; Wu and Wu, Biotherapy 3:87-95 (1991);



Tolstoshev, *Ann. Rev. Pharmacol. Toxicol.* 32:573-596 (1993); Mulligan, *Science* 260:926-932 (1993); and Morgan and Anderson, *Ann. Rev. Biochem.* 62:191-217 (1993); May, 1993, *TIB TECH* 11(5):155-215; and hygromycin (Santerre et al., *Gene* 30:147 (1984)). Methods commonly known in the art of recombinant DNA technology may be routinely applied to select the desired recombinant clone, and such methods are described, for example, in Ausubel et al. (eds.), *Current Protocols in Molecular Biology*, John Wiley & Sons, NY (1993); Kriegler, *Gene Transfer and Expression, A Laboratory Manual*, Stockton Press, NY (1990); and in Chapters 12 and 13, Dracopoli et al. (eds), *Current Protocols in Human Genetics*, John Wiley & Sons, NY (1994); Colberre-Garapin et al., *J. Mol. Biol.* 150:1 (1981), which are incorporated by reference herein in their entireties.

The expression levels of an antibody molecule can be increased by vector amplification (for a review, see Bebbington and Hentschel, *The use of vectors based on gene amplification for the expression of cloned genes in mammalian cells in DNA cloning*, Vol.3. (Academic Press, New York, 1987)). When a marker in the vector system expressing antibody is amplifiable, increase in the level of inhibitor present in culture of host cell will increase the number of copies of the marker gene. Since the amplified region is associated with the antibody gene, production of the antibody will also increase (Crouse et al., *Mol. Cell. Biol.* 3:257 (1983)).

The host cell may be co-transfected with two expression vectors of the invention, the first vector encoding a heavy chain derived polypeptide and the second vector encoding a light chain derived polypeptide. The two vectors may contain identical selectable markers which enable equal expression of heavy and light chain polypeptides. Alternatively, a single vector may be used which encodes, and is capable of expressing, both heavy and light chain polypeptides. In such situations, the light chain should be placed before the heavy chain to avoid an excess of toxic free heavy chain (Proudfoot, *Nature* 322:52 (1986); Kohler, *Proc. Natl. Acad. Sci. USA* 77:2197 (1980)). The coding sequences for the heavy and light chains may comprise cDNA or genomic DNA.

Once an antibody molecule of the invention has been produced by an animal, chemically synthesized, or recombinantly expressed, it may be purified by any method known in the art for purification of an immunoglobulin molecule, for example, by chromatography (e.g., ion exchange, affinity, particularly by affinity for  
5 the specific antigen after Protein A, and sizing column chromatography), centrifugation, differential solubility, or by any other standard technique for the purification of proteins. In addition, the antibodies of the present invention or fragments thereof can be fused to heterologous polypeptide sequences described herein or otherwise known in the art, to facilitate purification.

10 The present invention encompasses antibodies recombinantly fused or chemically conjugated (including both covalently and non-covalently conjugations) to a polypeptide (or portion thereof, preferably at least 10, 20, 30, 40, 50, 60, 70, 80, 90 or 100 amino acids of the polypeptide) of the present invention to generate fusion proteins. The fusion does not necessarily need to be direct, but may occur through  
15 linker sequences. The antibodies may be specific for antigens other than polypeptides (or portion thereof, preferably at least 10, 20, 30, 40, 50, 60, 70, 80, 90 or 100 amino acids of the polypeptide) of the present invention. For example, antibodies may be used to target the polypeptides of the present invention to particular cell types, either in vitro or in vivo, by fusing or conjugating the polypeptides of the present invention  
20 to antibodies specific for particular cell surface receptors. Antibodies fused or conjugated to the polypeptides of the present invention may also be used in in vitro immunoassays and purification methods using methods known in the art. See e.g., Harbor et al., supra, and PCT publication WO 93/21232; EP 439,095; Naramura et al., Immunol. Lett. 39:91-99 (1994); U.S. Patent 5,474,981; Gillies et al., PNAS  
25 89:1428-1432 (1992); Fell et al., J. Immunol. 146:2446-2452(1991), which are incorporated by reference in their entireties.

The present invention further includes compositions comprising the polypeptides of the present invention fused or conjugated to antibody domains other than the variable regions. For example, the polypeptides of the present invention may  
30 be fused or conjugated to an antibody Fc region, or portion thereof. The antibody

portion fused to a polypeptide of the present invention may comprise the constant region, hinge region, CH1 domain, CH2 domain, and CH3 domain or any combination of whole domains or portions thereof. The polypeptides may also be fused or conjugated to the above antibody portions to form multimers. For example, 5 Fc portions fused to the polypeptides of the present invention can form dimers through disulfide bonding between the Fc portions. Higher multimeric forms can be made by fusing the polypeptides to portions of IgA and IgM. Methods for fusing or conjugating the polypeptides of the present invention to antibody portions are known in the art. See, e.g., U.S. Patent Nos. 5,336,603; 5,622,929; 5,359,046; 5,349,053; 10 5,447,851; 5,112,946; EP 307,434; EP 367,166; PCT publications WO 96/04388; WO 91/06570; Ashkenazi et al., Proc. Natl. Acad. Sci. USA 88:10535-10539 (1991); Zheng et al., J. Immunol. 154:5590-5600 (1995); and Vil et al., Proc. Natl. Acad. Sci. USA 89:11337- 11341(1992) (said references incorporated by reference in their entirety).

15 As discussed, supra, the polypeptides corresponding to a polypeptide, polypeptide fragment, or a variant of SEQ ID NO:Y may be fused or conjugated to the above antibody portions to increase the in vivo half life of the polypeptides or for use in immunoassays using methods known in the art. Further, the polypeptides corresponding to SEQ ID NO:Y may be fused or conjugated to the above antibody 20 portions to facilitate purification. One reported example describes chimeric proteins consisting of the first two domains of the human CD4-polypeptide and various domains of the constant regions of the heavy or light chains of mammalian immunoglobulins. (EP 394,827; Traunecker et al., Nature 331:84-86 (1988). The polypeptides of the present invention fused or conjugated to an antibody having 25 disulfide- linked dimeric structures (due to the IgG) may also be more efficient in binding and neutralizing other molecules, than the monomeric secreted protein or protein fragment alone. (Fountoulakis et al., J. Biochem. 270:3958-3964 (1995)). In many cases, the Fc part in a fusion protein is beneficial in therapy and diagnosis, and thus can result in, for example, improved pharmacokinetic properties. (EP A 30 232,262). Alternatively, deleting the Fc part after the fusion protein has been

expressed, detected, and purified, would be desired. For example, the Fc portion may hinder therapy and diagnosis if the fusion protein is used as an antigen for immunizations. In drug discovery, for example, human proteins, such as hIL-5, have been fused with Fc portions for the purpose of high-throughput screening assays to identify antagonists of hIL-5. (See, Bennett et al., *J. Molecular Recognition* 8:52-58 (1995); Johanson et al., *J. Biol. Chem.* 270:9459-9471 (1995).

Moreover, the antibodies or fragments thereof of the present invention can be fused to marker sequences, such as a peptide to facilitate purification. In preferred embodiments, the marker amino acid sequence is a hexa-histidine peptide, such as the tag provided in a pQE vector (QIAGEN, Inc., 9259 Eton Avenue, Chatsworth, CA, 91311), among others, many of which are commercially available. As described in Gentz et al., *Proc. Natl. Acad. Sci. USA* 86:821-824 (1989), for instance, hexa-histidine provides for convenient purification of the fusion protein. Other peptide tags useful for purification include, but are not limited to, the "HA" tag, which corresponds to an epitope derived from the influenza hemagglutinin protein (Wilson et al., *Cell* 37:767 (1984)) and the "flag" tag.

The present invention further encompasses antibodies or fragments thereof conjugated to a diagnostic or therapeutic agent. The antibodies can be used diagnostically to, for example, monitor the development or progression of a tumor as part of a clinical testing procedure to, e.g., determine the efficacy of a given treatment regimen. Detection can be facilitated by coupling the antibody to a detectable substance. Examples of detectable substances include various enzymes, prosthetic groups, fluorescent materials, luminescent materials, bioluminescent materials, radioactive materials, positron emitting metals using various positron emission tomographies, and nonradioactive paramagnetic metal ions. The detectable substance may be coupled or conjugated either directly to the antibody (or fragment thereof) or indirectly, through an intermediate (such as, for example, a linker known in the art) using techniques known in the art. See, for example, U.S. Patent No. 4,741,900 for metal ions which can be conjugated to antibodies for use as diagnostics according to the present invention. Examples of suitable enzymes include horseradish

peroxidase, alkaline phosphatase, beta-galactosidase, or acetylcholinesterase; examples of suitable prosthetic group complexes include streptavidin/biotin and avidin/biotin; examples of suitable fluorescent materials include umbelliferone, fluorescein, fluorescein isothiocyanate, rhodamine, dichlorotriazinylamine  
5 fluorescein, dansyl chloride or phycoerythrin; an example of a luminescent material includes luminol; examples of bioluminescent materials include luciferase, luciferin, and aequorin; and examples of suitable radioactive material include <sup>125</sup>I, <sup>131</sup>I, <sup>111</sup>In or <sup>99</sup>Tc.

Further, an antibody or fragment thereof may be conjugated to a therapeutic  
10 moiety such as a cytotoxin, e.g., a cytostatic or cytotoxic agent, a therapeutic agent or a radioactive metal ion, e.g., alpha-emitters such as, for example, <sup>213</sup>Bi. A cytotoxin or cytotoxic agent includes any agent that is detrimental to cells. Examples include paclitaxol, cytochalasin B, gramicidin D, ethidium bromide, emetine, mitomycin, etoposide, tenoposide, vincristine, vinblastine, colchicin, doxorubicin, daunorubicin,  
15 dihydroxy anthracin dione, mitoxantrone, mithramycin, actinomycin D, 1-dehydrotestosterone, glucocorticoids, procaine, tetracaine, lidocaine, propranolol, and puromycin and analogs or homologs thereof. Therapeutic agents include, but are not limited to, antimetabolites (e.g., methotrexate, 6-mercaptopurine, 6-thioguanine, cytarabine, 5-fluorouracil decarbazine), alkylating agents (e.g., mechlorethamine,  
20 thioepa chlorambucil, melphalan, carmustine (BSNU) and lomustine (CCNU), cyclophosphamide, busulfan, dibromomannitol, streptozotocin, mitomycin C, and cis-dichlorodiamine platinum (II) (DDP) cisplatin), anthracyclines (e.g., daunorubicin (formerly daunomycin) and doxorubicin), antibiotics (e.g., dactinomycin (formerly actinomycin), bleomycin, mithramycin, and anthramycin (AMC)), and anti-mitotic  
25 agents (e.g., vincristine and vinblastine).

The conjugates of the invention can be used for modifying a given biological response, the therapeutic agent or drug moiety is not to be construed as limited to classical chemical therapeutic agents. For example, the drug moiety may be a protein or polypeptide possessing a desired biological activity. Such proteins may include,  
30 for example, a toxin such as abrin, ricin A, pseudomonas exotoxin, or diphtheria

toxin; a protein such as tumor necrosis factor,  $\alpha$ -interferon,  $\beta$ -interferon, nerve growth factor, platelet derived growth factor, tissue plasminogen activator, an apoptotic agent, e.g., TNF- $\alpha$ , TNF- $\beta$ , AIM I (See, International Publication No. WO 97/33899), AIM II (See, International Publication No. WO 97/34911), Fas  
5 Ligand (Takahashi *et al.*, *Int. Immunol.*, 6:1567-1574 (1994)), VEGF (See, International Publication No. WO 99/23105), a thrombotic agent or an anti-angiogenic agent, e.g., angiostatin or endostatin; or, biological response modifiers such as, for example, lymphokines, interleukin-1 ("IL-1"), interleukin-2 ("IL-2"), interleukin-6 ("IL-6"), granulocyte macrophage colony stimulating factor ("GM-  
10 CSF"), granulocyte colony stimulating factor ("G-CSF"), or other growth factors.

Antibodies may also be attached to solid supports, which are particularly useful for immunoassays or purification of the target antigen. Such solid supports include, but are not limited to, glass, cellulose, polyacrylamide, nylon, polystyrene, polyvinyl chloride or polypropylene.

15 Techniques for conjugating such therapeutic moiety to antibodies are well known, see, e.g., Arnon *et al.*, "Monoclonal Antibodies For Immunotargeting Of Drugs In Cancer Therapy", in *Monoclonal Antibodies And Cancer Therapy*, Reisfeld *et al.* (eds.), pp. 243-56 (Alan R. Liss, Inc. 1985); Hellstrom *et al.*, "Antibodies For Drug Delivery", in *Controlled Drug Delivery* (2nd Ed.), Robinson *et al.* (eds.), pp.  
20 623-53 (Marcel Dekker, Inc. 1987); Thorpe, "Antibody Carriers Of Cytotoxic Agents In Cancer Therapy: A Review", in *Monoclonal Antibodies '84: Biological And Clinical Applications*, Pinchera *et al.* (eds.), pp. 475-506 (1985); "Analysis, Results, And Future Prospective Of The Therapeutic Use Of Radiolabeled Antibody In Cancer Therapy", in *Monoclonal Antibodies For Cancer Detection And Therapy*,  
25 Baldwin *et al.* (eds.), pp. 303-16 (Academic Press 1985), and Thorpe *et al.*, "The Preparation And Cytotoxic Properties Of Antibody-Toxin Conjugates", *Immunol. Rev.* 62:119-58 (1982).

Alternatively, an antibody can be conjugated to a second antibody to form an antibody heteroconjugate as described by Segal in U.S. Patent No. 4,676,980, which  
30 is incorporated herein by reference in its entirety.

An antibody, with or without a therapeutic moiety conjugated to it, administered alone or in combination with cytotoxic factor(s) and/or cytokine(s) can be used as a therapeutic.

## 5 *Immunophenotyping*

The antibodies of the invention may be utilized for immunophenotyping of cell lines and biological samples. The translation product of the gene of the present invention may be useful as a cell specific marker, or more specifically as a cellular marker that is differentially expressed at various stages of differentiation and/or  
10 maturation of particular cell types. Monoclonal antibodies directed against a specific epitope, or combination of epitopes, will allow for the screening of cellular populations expressing the marker. Various techniques can be utilized using monoclonal antibodies to screen for cellular populations expressing the marker(s), and include magnetic separation using antibody-coated magnetic beads, "panning"  
15 with antibody attached to a solid matrix (i.e., plate), and flow cytometry (See, e.g., U.S. Patent 5,985,660; and Morrison *et al.*, *Cell*, 96:737-49 (1999)).

These techniques allow for the screening of particular populations of cells, such as might be found with hematological malignancies (i.e. minimal residual disease (MRD) in acute leukemic patients) and "non-self" cells in transplantations to  
20 prevent Graft-versus-Host Disease (GVHD). Alternatively, these techniques allow for the screening of hematopoietic stem and progenitor cells capable of undergoing proliferation and/or differentiation, as might be found in human umbilical cord blood.

## *Assays For Antibody Binding*

25 The antibodies of the invention may be assayed for immunospecific binding by any method known in the art. The immunoassays which can be used include but are not limited to competitive and non-competitive assay systems using techniques such as western blots, radioimmunoassays, ELISA (enzyme linked immunosorbent assay), "sandwich" immunoassays, immunoprecipitation assays, precipitin reactions,  
30 gel diffusion precipitin reactions, immunodiffusion assays, agglutination assays,

complement-fixation assays, immunoradiometric assays, fluorescent immunoassays, protein A immunoassays, to name but a few. Such assays are routine and well known in the art (see, e.g., Ausubel et al, eds, 1994, Current Protocols in Molecular Biology, Vol. 1, John Wiley & Sons, Inc., New York, which is incorporated by  
5 reference herein in its entirety). Exemplary immunoassays are described briefly below (but are not intended by way of limitation).

Immunoprecipitation protocols generally comprise lysing a population of cells in a lysis buffer such as RIPA buffer (1% NP-40 or Triton X- 100, 1% sodium deoxycholate, 0.1% SDS, 0.15 M NaCl, 0.01 M sodium phosphate at pH 7.2, 1%  
10 Trasylol) supplemented with protein phosphatase and/or protease inhibitors (e.g., EDTA, PMSF, aprotinin, sodium vanadate), adding the antibody of interest to the cell lysate, incubating for a period of time (e.g., 1-4 hours) at 4° C, adding protein A and/or protein G sepharose beads to the cell lysate, incubating for about an hour or more at 4° C, washing the beads in lysis buffer and resuspending the beads in  
15 SDS/sample buffer. The ability of the antibody of interest to immunoprecipitate a particular antigen can be assessed by, e.g., western blot analysis. One of skill in the art would be knowledgeable as to the parameters that can be modified to increase the binding of the antibody to an antigen and decrease the background (e.g., pre-clearing the cell lysate with sepharose beads). For further discussion regarding  
20 immunoprecipitation protocols see, e.g., Ausubel et al, eds, 1994, Current Protocols in Molecular Biology, Vol. 1, John Wiley & Sons, Inc., New York at 10.16.1.

Western blot analysis generally comprises preparing protein samples, electrophoresis of the protein samples in a polyacrylamide gel (e.g., 8%- 20% SDS-PAGE depending on the molecular weight of the antigen), transferring the protein  
25 sample from the polyacrylamide gel to a membrane such as nitrocellulose, PVDF or nylon, blocking the membrane in blocking solution (e.g., PBS with 3% BSA or non-fat milk), washing the membrane in washing buffer (e.g., PBS-Tween 20), blocking the membrane with primary antibody (the antibody of interest) diluted in blocking buffer, washing the membrane in washing buffer, blocking the membrane with a  
30 secondary antibody (which recognizes the primary antibody, e.g., an anti-human



antibody) conjugated to an enzymatic substrate (e.g., horseradish peroxidase or alkaline phosphatase) or radioactive molecule (e.g.,  $^{32}\text{P}$  or  $^{125}\text{I}$ ) diluted in blocking buffer, washing the membrane in wash buffer, and detecting the presence of the antigen. One of skill in the art would be knowledgeable as to the parameters that can be modified to increase the signal detected and to reduce the background noise. For further discussion regarding western blot protocols see, e.g., Ausubel et al, eds, 1994, Current Protocols in Molecular Biology, Vol. 1, John Wiley & Sons, Inc., New York at 10.8.1.

ELISAs comprise preparing antigen, coating the well of a 96 well microtiter plate with the antigen, adding the antibody of interest conjugated to a detectable compound such as an enzymatic substrate (e.g., horseradish peroxidase or alkaline phosphatase) to the well and incubating for a period of time, and detecting the presence of the antigen. In ELISAs the antibody of interest does not have to be conjugated to a detectable compound; instead, a second antibody (which recognizes the antibody of interest) conjugated to a detectable compound may be added to the well. Further, instead of coating the well with the antigen, the antibody may be coated to the well. In this case, a second antibody conjugated to a detectable compound may be added following the addition of the antigen of interest to the coated well. One of skill in the art would be knowledgeable as to the parameters that can be modified to increase the signal detected as well as other variations of ELISAs known in the art. For further discussion regarding ELISAs see, e.g., Ausubel et al, eds, 1994, Current Protocols in Molecular Biology, Vol. 1, John Wiley & Sons, Inc., New York at 11.2.1.

The binding affinity of an antibody to an antigen and the off-rate of an antibody-antigen interaction can be determined by competitive binding assays. One example of a competitive binding assay is a radioimmunoassay comprising the incubation of labeled antigen (e.g.,  $^3\text{H}$  or  $^{125}\text{I}$ ) with the antibody of interest in the presence of increasing amounts of unlabeled antigen, and the detection of the antibody bound to the labeled antigen. The affinity of the antibody of interest for a particular antigen and the binding off-rates can be determined from the data by

scatchard plot analysis. Competition with a second antibody can also be determined using radioimmunoassays. In this case, the antigen is incubated with antibody of interest conjugated to a labeled compound (e.g.,  $^3\text{H}$  or  $^{125}\text{I}$ ) in the presence of increasing amounts of an unlabeled second antibody.

5

### *Therapeutic Uses*

The present invention is further directed to antibody-based therapies which involve administering antibodies of the invention to an animal, preferably a mammal, and most preferably a human, patient for treating one or more of the disclosed  
10 diseases, disorders, or conditions. Therapeutic compounds of the invention include, but are not limited to, antibodies of the invention (including fragments, analogs and derivatives thereof as described herein) and nucleic acids encoding antibodies of the invention (including fragments, analogs and derivatives thereof and anti-idiotypic antibodies as described herein). The antibodies of the invention can be used to treat,  
15 inhibit or prevent diseases, disorders or conditions associated with aberrant expression and/or activity of a polypeptide of the invention, including, but not limited to, any one or more of the diseases, disorders, or conditions described herein. The treatment and/or prevention of diseases, disorders, or conditions associated with aberrant expression and/or activity of a polypeptide of the invention includes, but is  
20 not limited to, alleviating symptoms associated with those diseases, disorders or conditions. Antibodies of the invention may be provided in pharmaceutically acceptable compositions as known in the art or as described herein.

A summary of the ways in which the antibodies of the present invention may be used therapeutically includes binding polynucleotides or polypeptides of the  
25 present invention locally or systemically in the body or by direct cytotoxicity of the antibody, e.g. as mediated by complement (CDC) or by effector cells (ADCC). Some of these approaches are described in more detail below. Armed with the teachings provided herein, one of ordinary skill in the art will know how to use the antibodies of the present invention for diagnostic, monitoring or therapeutic purposes  
30 without undue experimentation.

The antibodies of this invention may be advantageously utilized in combination with other monoclonal or chimeric antibodies, or with lymphokines or hematopoietic growth factors (such as, e.g., IL-2, IL-3 and IL-7), for example, which serve to increase the number or activity of effector cells which interact with the antibodies.

The antibodies of the invention may be administered alone or in combination with other types of treatments (e.g., radiation therapy, chemotherapy, hormonal therapy, immunotherapy and anti-tumor agents). Generally, administration of products of a species origin or species reactivity (in the case of antibodies) that is the same species as that of the patient is preferred. Thus, in a preferred embodiment, human antibodies, fragments derivatives, analogs, or nucleic acids, are administered to a human patient for therapy or prophylaxis.

It is preferred to use high affinity and/or potent in vivo inhibiting and/or neutralizing antibodies against polypeptides or polynucleotides of the present invention, fragments or regions thereof, for both immunoassays directed to and therapy of disorders related to polynucleotides or polypeptides, including fragments thereof, of the present invention. Such antibodies, fragments, or regions, will preferably have an affinity for polynucleotides or polypeptides of the invention, including fragments thereof. Preferred binding affinities include those with a dissociation constant or  $K_d$  less than  $5 \times 10^{-2}$  M,  $10^{-2}$  M,  $5 \times 10^{-3}$  M,  $10^{-3}$  M,  $5 \times 10^{-4}$  M,  $10^{-4}$  M,  $5 \times 10^{-5}$  M,  $10^{-5}$  M,  $5 \times 10^{-6}$  M,  $10^{-6}$  M,  $5 \times 10^{-7}$  M,  $10^{-7}$  M,  $5 \times 10^{-8}$  M,  $10^{-8}$  M,  $5 \times 10^{-9}$  M,  $10^{-9}$  M,  $5 \times 10^{-10}$  M,  $10^{-10}$  M,  $5 \times 10^{-11}$  M,  $10^{-11}$  M,  $5 \times 10^{-12}$  M,  $10^{-12}$  M,  $5 \times 10^{-13}$  M,  $10^{-13}$  M,  $5 \times 10^{-14}$  M,  $10^{-14}$  M,  $5 \times 10^{-15}$  M, and  $10^{-15}$  M.

## 25 *Gene Therapy*

In a specific embodiment, nucleic acids comprising sequences encoding antibodies or functional derivatives thereof, are administered to treat, inhibit or prevent a disease or disorder associated with aberrant expression and/or activity of a polypeptide of the invention, by way of gene therapy. Gene therapy refers to therapy performed by the administration to a subject of an expressed or expressible nucleic

acid. In this embodiment of the invention, the nucleic acids produce their encoded protein that mediates a therapeutic effect.

Any of the methods for gene therapy available in the art can be used according to the present invention. Exemplary methods are described below.

5 For general reviews of the methods of gene therapy, see Goldspiel et al., Clinical Pharmacy 12:488-505 (1993); Wu and Wu, Biotherapy 3:87-95 (1991); Tolstoshev, Ann. Rev. Pharmacol. Toxicol. 32:573-596 (1993); Mulligan, Science 260:926-932 (1993); and Morgan and Anderson, Ann. Rev. Biochem. 62:191-217 (1993); May, TIBTECH 11(5):155-215 (1993). Methods commonly known in the art  
10 of recombinant DNA technology which can be used are described in Ausubel et al. (eds.), Current Protocols in Molecular Biology, John Wiley & Sons, NY (1993); and Kriegler, Gene Transfer and Expression, A Laboratory Manual, Stockton Press, NY (1990).

In a preferred aspect, the compound comprises nucleic acid sequences  
15 encoding an antibody, said nucleic acid sequences being part of expression vectors that express the antibody or fragments or chimeric proteins or heavy or light chains thereof in a suitable host. In particular, such nucleic acid sequences have promoters operably linked to the antibody coding region, said promoter being inducible or constitutive, and, optionally, tissue-specific. In another particular embodiment,  
20 nucleic acid molecules are used in which the antibody coding sequences and any other desired sequences are flanked by regions that promote homologous recombination at a desired site in the genome, thus providing for intrachromosomal expression of the antibody encoding nucleic acids (Koller and Smithies, Proc. Natl. Acad. Sci. USA 86:8932-8935 (1989); Zijlstra et al., Nature 342:435-438 (1989). In  
25 specific embodiments, the expressed antibody molecule is a single chain antibody; alternatively, the nucleic acid sequences include sequences encoding both the heavy and light chains, or fragments thereof, of the antibody.

Delivery of the nucleic acids into a patient may be either direct, in which case the patient is directly exposed to the nucleic acid or nucleic acid-carrying vectors, or  
30 indirect, in which case, cells are first transformed with the nucleic acids in vitro, then

transplanted into the patient. These two approaches are known, respectively, as in vivo or ex vivo gene therapy.

In a specific embodiment, the nucleic acid sequences are directly administered in vivo, where it is expressed to produce the encoded product. This can be accomplished by any of numerous methods known in the art, e.g., by constructing them as part of an appropriate nucleic acid expression vector and administering it so that they become intracellular, e.g., by infection using defective or attenuated retrovirals or other viral vectors (see U.S. Patent No. 4,980,286), or by direct injection of naked DNA, or by use of microparticle bombardment (e.g., a gene gun; Biolistic, Dupont), or coating with lipids or cell-surface receptors or transfecting agents, encapsulation in liposomes, microparticles, or microcapsules, or by administering them in linkage to a peptide which is known to enter the nucleus, by administering it in linkage to a ligand subject to receptor-mediated endocytosis (see, e.g., Wu and Wu, J. Biol. Chem. 262:4429-4432 (1987)) (which can be used to target cell types specifically expressing the receptors), etc. In another embodiment, nucleic acid-ligand complexes can be formed in which the ligand comprises a fusogenic viral peptide to disrupt endosomes, allowing the nucleic acid to avoid lysosomal degradation. In yet another embodiment, the nucleic acid can be targeted in vivo for cell specific uptake and expression, by targeting a specific receptor (see, e.g., PCT Publications WO 92/06180; WO 92/22635; WO92/20316; WO93/14188, WO 93/20221). Alternatively, the nucleic acid can be introduced intracellularly and incorporated within host cell DNA for expression, by homologous recombination (Koller and Smithies, Proc. Natl. Acad. Sci. USA 86:8932-8935 (1989); Zijlstra et al., Nature 342:435-438 (1989)).

In a specific embodiment, viral vectors that contains nucleic acid sequences encoding an antibody of the invention are used. For example, a retroviral vector can be used (see Miller et al., Meth. Enzymol. 217:581-599 (1993)). These retroviral vectors contain the components necessary for the correct packaging of the viral genome and integration into the host cell DNA. The nucleic acid sequences encoding the antibody to be used in gene therapy are cloned into one or more vectors, which

facilitates delivery of the gene into a patient. More detail about retroviral vectors can be found in Boesen et al., *Biotherapy* 6:291-302 (1994), which describes the use of a retroviral vector to deliver the *mdrl* gene to hematopoietic stem cells in order to make the stem cells more resistant to chemotherapy. Other references illustrating the use of retroviral vectors in gene therapy are: Clowes et al., *J. Clin. Invest.* 93:644-651 (1994); Kiem et al., *Blood* 83:1467-1473 (1994); Salmons and Gunzberg, *Human Gene Therapy* 4:129-141 (1993); and Grossman and Wilson, *Curr. Opin. in Genetics and Devel.* 3:110-114 (1993).

Adenoviruses are other viral vectors that can be used in gene therapy. Adenoviruses are especially attractive vehicles for delivering genes to respiratory epithelia. Adenoviruses naturally infect respiratory epithelia where they cause a mild disease. Other targets for adenovirus-based delivery systems are liver, the central nervous system, endothelial cells, and muscle. Adenoviruses have the advantage of being capable of infecting non-dividing cells. Kozarsky and Wilson, *Current Opinion in Genetics and Development* 3:499-503 (1993) present a review of adenovirus-based gene therapy. Bout et al., *Human Gene Therapy* 5:3-10 (1994) demonstrated the use of adenovirus vectors to transfer genes to the respiratory epithelia of rhesus monkeys. Other instances of the use of adenoviruses in gene therapy can be found in Rosenfeld et al., *Science* 252:431-434 (1991); Rosenfeld et al., *Cell* 68:143-155 (1992); Mastrangeli et al., *J. Clin. Invest.* 91:225-234 (1993); PCT Publication WO94/12649; and Wang, et al., *Gene Therapy* 2:775-783 (1995). In a preferred embodiment, adenovirus vectors are used.

Adeno-associated virus (AAV) has also been proposed for use in gene therapy (Walsh et al., *Proc. Soc. Exp. Biol. Med.* 204:289-300 (1993); U.S. Patent No. 5,436,146).

Another approach to gene therapy involves transferring a gene to cells in tissue culture by such methods as electroporation, lipofection, calcium phosphate mediated transfection, or viral infection. Usually, the method of transfer includes the transfer of a selectable marker to the cells. The cells are then placed under selection

to isolate those cells that have taken up and are expressing the transferred gene. Those cells are then delivered to a patient.

In this embodiment, the nucleic acid is introduced into a cell prior to administration in vivo of the resulting recombinant cell. Such introduction can be carried out by any method known in the art, including but not limited to transfection, electroporation, microinjection, infection with a viral or bacteriophage vector containing the nucleic acid sequences, cell fusion, chromosome-mediated gene transfer, microcell-mediated gene transfer, spheroplast fusion, etc. Numerous techniques are known in the art for the introduction of foreign genes into cells (see, e.g., Loeffler and Behr, *Meth. Enzymol.* 217:599-618 (1993); Cohen et al., *Meth. Enzymol.* 217:618-644 (1993); Cline, *Pharmac. Ther.* 29:69-92m (1985) and may be used in accordance with the present invention, provided that the necessary developmental and physiological functions of the recipient cells are not disrupted. The technique should provide for the stable transfer of the nucleic acid to the cell, so that the nucleic acid is expressible by the cell and preferably heritable and expressible by its cell progeny.

The resulting recombinant cells can be delivered to a patient by various methods known in the art. Recombinant blood cells (e.g., hematopoietic stem or progenitor cells) are preferably administered intravenously. The amount of cells envisioned for use depends on the desired effect, patient state, etc., and can be determined by one skilled in the art.

Cells into which a nucleic acid can be introduced for purposes of gene therapy encompass any desired, available cell type, and include but are not limited to epithelial cells, endothelial cells, keratinocytes, fibroblasts, muscle cells, hepatocytes; blood cells such as Tlymphocytes, Blymphocytes, monocytes, macrophages, neutrophils, eosinophils, megakaryocytes, granulocytes; various stem or progenitor cells, in particular hematopoietic stem or progenitor cells, e.g., as obtained from bone marrow, umbilical cord blood, peripheral blood, fetal liver, etc.

In a preferred embodiment, the cell used for gene therapy is autologous to the patient.

In an embodiment in which recombinant cells are used in gene therapy, nucleic acid sequences encoding an antibody are introduced into the cells such that they are expressible by the cells or their progeny, and the recombinant cells are then administered in vivo for therapeutic effect. In a specific embodiment, stem or progenitor cells are used. Any stem and/or progenitor cells which can be isolated and maintained in vitro can potentially be used in accordance with this embodiment of the present invention (see e.g. PCT Publication WO 94/08598; Stemple and Anderson, Cell 71:973-985 (1992); Rheinwald, Meth. Cell Bio. 21A:229 (1980); and Pittelkow and Scott, Mayo Clinic Proc. 61:771 (1986)).

10 In a specific embodiment, the nucleic acid to be introduced for purposes of gene therapy comprises an inducible promoter operably linked to the coding region, such that expression of the nucleic acid is controllable by controlling the presence or absence of the appropriate inducer of transcription. Demonstration of Therapeutic or Prophylactic Activity

15 The compounds or pharmaceutical compositions of the invention are preferably tested in vitro, and then in vivo for the desired therapeutic or prophylactic activity, prior to use in humans. For example, in vitro assays to demonstrate the therapeutic or prophylactic utility of a compound or pharmaceutical composition include, the effect of a compound on a cell line or a patient tissue sample. The effect of the compound or composition on the cell line and/or tissue sample can be determined utilizing techniques known to those of skill in the art including, but not limited to, rosette formation assays and cell lysis assays. In accordance with the invention, in vitro assays which can be used to determine whether administration of a specific compound is indicated, include in vitro cell culture assays in which a patient tissue sample is grown in culture, and exposed to or otherwise administered a compound, and the effect of such compound upon the tissue sample is observed.

#### ***Therapeutic/Prophylactic Administration and Composition***

30 The invention provides methods of treatment, inhibition and prophylaxis by administration to a subject of an effective amount of a compound or pharmaceutical



composition of the invention, preferably a polypeptide or antibody of the invention. In a preferred aspect, the compound is substantially purified (e.g., substantially free from substances that limit its effect or produce undesired side-effects). The subject is preferably an animal, including but not limited to animals such as cows, pigs, horses,  
5 chickens, cats, dogs, etc., and is preferably a mammal, and most preferably human.

Formulations and methods of administration that can be employed when the compound comprises a nucleic acid or an immunoglobulin are described above; additional appropriate formulations and routes of administration can be selected from among those described herein below.

10 Various delivery systems are known and can be used to administer a compound of the invention, e.g., encapsulation in liposomes, microparticles, microcapsules, recombinant cells capable of expressing the compound, receptor-mediated endocytosis (see, e.g., Wu and Wu, J. Biol. Chem. 262:4429-4432 (1987)), construction of a nucleic acid as part of a retroviral or other vector, etc. Methods of  
15 introduction include but are not limited to intradermal, intramuscular, intraperitoneal, intravenous, subcutaneous, intranasal, epidural, and oral routes. The compounds or compositions may be administered by any convenient route, for example by infusion or bolus injection, by absorption through epithelial or mucocutaneous linings (e.g., oral mucosa, rectal and intestinal mucosa, etc.) and may be administered together  
20 with other biologically active agents. Administration can be systemic or local. In addition, it may be desirable to introduce the pharmaceutical compounds or compositions of the invention into the central nervous system by any suitable route, including intraventricular and intrathecal injection; intraventricular injection may be facilitated by an intraventricular catheter, for example, attached to a reservoir, such  
25 as an Ommaya reservoir. Pulmonary administration can also be employed, e.g., by use of an inhaler or nebulizer, and formulation with an aerosolizing agent.

In a specific embodiment, it may be desirable to administer the pharmaceutical compounds or compositions of the invention locally to the area in need of treatment; this may be achieved by, for example, and not by way of limitation, local infusion  
30 during surgery, topical application, e.g., in conjunction with a wound dressing after

surgery, by injection, by means of a catheter, by means of a suppository, or by means of an implant, said implant being of a porous, non-porous, or gelatinous material, including membranes, such as sialastic membranes, or fibers. Preferably, when administering a protein, including an antibody, of the invention, care must be taken  
5 to use materials to which the protein does not absorb.

In another embodiment, the compound or composition can be delivered in a vesicle, in particular a liposome (see Langer, *Science* 249:1527-1533 (1990); Treat et al., in *Liposomes in the Therapy of Infectious Disease and Cancer*, Lopez-Berestein and Fidler (eds.), Liss, New York, pp. 353- 365 (1989); Lopez-Berestein, *ibid.*, pp.  
10 317-327; see generally *ibid.*)

In yet another embodiment, the compound or composition can be delivered in a controlled release system. In one embodiment, a pump may be used (see Langer, *supra*; Sefton, *CRC Crit. Ref. Biomed. Eng.* 14:201 (1987); Buchwald et al., *Surgery* 88:507 (1980); Saudek et al., *N. Engl. J. Med.* 321:574 (1989)). In another  
15 embodiment, polymeric materials can be used (see *Medical Applications of Controlled Release*, Langer and Wise (eds.), CRC Pres., Boca Raton, Florida (1974); *Controlled Drug Bioavailability, Drug Product Design and Performance*, Smolen and Ball (eds.), Wiley, New York (1984); Ranger and Peppas, J., *Macromol. Sci. Rev. Macromol. Chem.* 23:61 (1983); see also Levy et al., *Science* 228:190 (1985); During  
20 et al., *Ann. Neurol.* 25:351 (1989); Howard et al., *J. Neurosurg.* 71:105 (1989)). In yet another embodiment, a controlled release system can be placed in proximity of the therapeutic target, i.e., the brain, thus requiring only a fraction of the systemic dose (see, e.g., Goodson, in *Medical Applications of Controlled Release*, *supra*, vol. 2, pp. 115-138 (1984)).

25 Other controlled release systems are discussed in the review by Langer (*Science* 249:1527-1533 (1990)).

In a specific embodiment where the compound of the invention is a nucleic acid encoding a protein, the nucleic acid can be administered *in vivo* to promote expression of its encoded protein, by constructing it as part of an appropriate nucleic  
30 acid expression vector and administering it so that it becomes intracellular, e.g., by

use of a retroviral vector (see U.S. Patent No. 4,980,286), or by direct injection. or by use of microparticle bombardment (e.g., a gene gun; Biolistic, Dupont), or coating with lipids or cell-surface receptors or transfecting agents, or by administering it in linkage to a homeobox- like peptide which is known to enter the nucleus (see e.g.,  
5 Joliot et al., Proc. Natl. Acad. Sci. USA 88:1864-1868 (1991)), etc. Alternatively, a nucleic acid can be introduced intracellularly and incorporated within host cell DNA for expression, by homologous recombination.

The present invention also provides pharmaceutical compositions. Such compositions comprise a therapeutically effective amount of a compound, and a  
10 pharmaceutically acceptable carrier. In a specific embodiment, the term "pharmaceutically acceptable" means approved by a regulatory agency of the Federal or a state government or listed in the U.S. Pharmacopeia or other generally recognized pharmacopeia for use in animals, and more particularly in humans. The term "carrier" refers to a diluent, adjuvant, excipient, or vehicle with which the  
15 therapeutic is administered. Such pharmaceutical carriers can be sterile liquids, such as water and oils, including those of petroleum, animal, vegetable or synthetic origin, such as peanut oil, soybean oil, mineral oil, sesame oil and the like. Water is a preferred carrier when the pharmaceutical composition is administered intravenously. Saline solutions and aqueous dextrose and glycerol solutions can also be employed as  
20 liquid carriers, particularly for injectable solutions. Suitable pharmaceutical excipients include starch, glucose, lactose, sucrose, gelatin, malt, rice, flour, chalk, silica gel, sodium stearate, glycerol monostearate, talc, sodium chloride, dried skim milk, glycerol, propylene, glycol, water, ethanol and the like. The composition, if desired, can also contain minor amounts of wetting or emulsifying agents, or pH  
25 buffering agents. These compositions can take the form of solutions, suspensions, emulsion, tablets, pills, capsules, powders, sustained-release formulations and the like. The composition can be formulated as a suppository, with traditional binders and carriers such as triglycerides. Oral formulation can include standard carriers such as pharmaceutical grades of mannitol, lactose, starch, magnesium stearate,  
30 sodium saccharine, cellulose, magnesium carbonate, etc. Examples of suitable

pharmaceutical carriers are described in "Remington's Pharmaceutical Sciences" by E.W. Martin. Such compositions will contain a therapeutically effective amount of the compound, preferably in purified form, together with a suitable amount of carrier so as to provide the form for proper administration to the patient. The formulation should suit the mode of administration.

In a preferred embodiment, the composition is formulated in accordance with routine procedures as a pharmaceutical composition adapted for intravenous administration to human beings. Typically, compositions for intravenous administration are solutions in sterile isotonic aqueous buffer. Where necessary, the composition may also include a solubilizing agent and a local anesthetic such as lignocaine to ease pain at the site of the injection. Generally, the ingredients are supplied either separately or mixed together in unit dosage form, for example, as a dry lyophilized powder or water free concentrate in a hermetically sealed container such as an ampoule or sachette indicating the quantity of active agent. Where the composition is to be administered by infusion, it can be dispensed with an infusion bottle containing sterile pharmaceutical grade water or saline. Where the composition is administered by injection, an ampoule of sterile water for injection or saline can be provided so that the ingredients may be mixed prior to administration.

The compounds of the invention can be formulated as neutral or salt forms. Pharmaceutically acceptable salts include those formed with anions such as those derived from hydrochloric, phosphoric, acetic, oxalic, tartaric acids, etc., and those formed with cations such as those derived from sodium, potassium, ammonium, calcium, ferric hydroxides, isopropylamine, triethylamine, 2-ethylamino ethanol, histidine, procaine, etc.

The amount of the compound of the invention which will be effective in the treatment, inhibition and prevention of a disease or disorder associated with aberrant expression and/or activity of a polypeptide of the invention can be determined by standard clinical techniques. In addition, in vitro assays may optionally be employed to help identify optimal dosage ranges. The precise dose to be employed in the formulation will also depend on the route of administration, and the seriousness of

the disease or disorder, and should be decided according to the judgment of the practitioner and each patient's circumstances. Effective doses may be extrapolated from dose-response curves derived from in vitro or animal model test systems.

For antibodies, the dosage administered to a patient is typically 0.1 mg/kg to 100 mg/kg of the patient's body weight. Preferably, the dosage administered to a patient is between 0.1 mg/kg and 20 mg/kg of the patient's body weight, more preferably 1 mg/kg to 10 mg/kg of the patient's body weight. Generally, human antibodies have a longer half-life within the human body than antibodies from other species due to the immune response to the foreign polypeptides. Thus, lower dosages of human antibodies and less frequent administration is often possible. Further, the dosage and frequency of administration of antibodies of the invention may be reduced by enhancing uptake and tissue penetration (e.g., into the brain) of the antibodies by modifications such as, for example, lipidation.

The invention also provides a pharmaceutical pack or kit comprising one or more containers filled with one or more of the ingredients of the pharmaceutical compositions of the invention. Optionally associated with such container(s) can be a notice in the form prescribed by a governmental agency regulating the manufacture, use or sale of pharmaceuticals or biological products, which notice reflects approval by the agency of manufacture, use or sale for human administration.

20

### ***Diagnosis and Imaging***

Labeled antibodies, and derivatives and analogs thereof, which specifically bind to a polypeptide of interest can be used for diagnostic purposes to detect, diagnose, or monitor diseases, disorders, and/or conditions associated with the aberrant expression and/or activity of a polypeptide of the invention. The invention provides for the detection of aberrant expression of a polypeptide of interest, comprising (a) assaying the expression of the polypeptide of interest in cells or body fluid of an individual using one or more antibodies specific to the polypeptide interest and (b) comparing the level of gene expression with a standard gene expression level,

whereby an increase or decrease in the assayed polypeptide gene expression level compared to the standard expression level is indicative of aberrant expression.

The invention provides a diagnostic assay for diagnosing a disorder, comprising (a) assaying the expression of the polypeptide of interest in cells or body  
5 fluid of an individual using one or more antibodies specific to the polypeptide interest and (b) comparing the level of gene expression with a standard gene expression level, whereby an increase or decrease in the assayed polypeptide gene expression level compared to the standard expression level is indicative of a particular disorder. With respect to cancer, the presence of a relatively high amount of transcript in biopsied  
10 tissue from an individual may indicate a predisposition for the development of the disease, or may provide a means for detecting the disease prior to the appearance of actual clinical symptoms. A more definitive diagnosis of this type may allow health professionals to employ preventative measures or aggressive treatment earlier thereby preventing the development or further progression of the cancer.

15 Antibodies of the invention can be used to assay protein levels in a biological sample using classical immunohistological methods known to those of skill in the art (e.g., see Jalkanen, et al., J. Cell. Biol. 101:976-985 (1985); Jalkanen, et al., J. Cell . Biol. 105:3087-3096 (1987)). Other antibody-based methods useful for detecting protein gene expression include immunoassays, such as the enzyme linked  
20 immunosorbent assay (ELISA) and the radioimmunoassay (RIA). Suitable antibody assay labels are known in the art and include enzyme labels, such as, glucose oxidase; radioisotopes, such as iodine (<sup>125</sup>I, <sup>121</sup>I), carbon (<sup>14</sup>C), sulfur (<sup>35</sup>S), tritium (<sup>3</sup>H), indium (<sup>112</sup>In), and technetium (<sup>99</sup>Tc); luminescent labels, such as luminol; and fluorescent labels, such as fluorescein and rhodamine, and biotin.

25 One aspect of the invention is the detection and diagnosis of a disease or disorder associated with aberrant expression of a polypeptide of interest in an animal, preferably a mammal and most preferably a human. In one embodiment, diagnosis comprises: a) administering (for example, parenterally, subcutaneously, or intraperitoneally) to a subject an effective amount of a labeled molecule which  
30 specifically binds to the polypeptide of interest; b) waiting for a time interval

following the administering for permitting the labeled molecule to preferentially concentrate at sites in the subject where the polypeptide is expressed (and for unbound labeled molecule to be cleared to background level); c) determining background level; and d) detecting the labeled molecule in the subject, such that  
5 detection of labeled molecule above the background level indicates that the subject has a particular disease or disorder associated with aberrant expression of the polypeptide of interest. Background level can be determined by various methods including, comparing the amount of labeled molecule detected to a standard value previously determined for a particular system.

10 It will be understood in the art that the size of the subject and the imaging system used will determine the quantity of imaging moiety needed to produce diagnostic images. In the case of a radioisotope moiety, for a human subject, the quantity of radioactivity injected will normally range from about 5 to 20 millicuries of <sup>99m</sup>Tc. The labeled antibody or antibody fragment will then preferentially  
15 accumulate at the location of cells which contain the specific protein. In vivo tumor imaging is described in S.W. Burchiel et al., "Immunopharmacokinetics of Radiolabeled Antibodies and Their Fragments." (Chapter 13 in Tumor Imaging: The Radiochemical Detection of Cancer, S.W. Burchiel and B. A. Rhodes, eds., Masson Publishing Inc. (1982).

20 Depending on several variables, including the type of label used and the mode of administration, the time interval following the administration for permitting the labeled molecule to preferentially concentrate at sites in the subject and for unbound labeled molecule to be cleared to background level is 6 to 48 hours or 6 to 24 hours or 6 to 12 hours. In another embodiment the time interval following administration is 5  
25 to 20 days or 5 to 10 days.

In an embodiment, monitoring of the disease or disorder is carried out by repeating the method for diagnosing the disease or disease, for example, one month after initial diagnosis, six months after initial diagnosis, one year after initial diagnosis, etc.

Presence of the labeled molecule can be detected in the patient using methods known in the art for in vivo scanning. These methods depend upon the type of label used. Skilled artisans will be able to determine the appropriate method for detecting a particular label. Methods and devices that may be used in the diagnostic methods of the invention include, but are not limited to, computed tomography (CT), whole body scan such as position emission tomography (PET), magnetic resonance imaging (MRI), and sonography.

In a specific embodiment, the molecule is labeled with a radioisotope and is detected in the patient using a radiation responsive surgical instrument (Thurston et al., U.S. Patent No. 5,441,050). In another embodiment, the molecule is labeled with a fluorescent compound and is detected in the patient using a fluorescence responsive scanning instrument. In another embodiment, the molecule is labeled with a positron emitting metal and is detected in the patient using positron emission-tomography. In yet another embodiment, the molecule is labeled with a paramagnetic label and is detected in a patient using magnetic resonance imaging (MRI).

### ***Kits***

The present invention provides kits that can be used in the above methods. In one embodiment, a kit comprises an antibody of the invention, preferably a purified antibody, in one or more containers. In a specific embodiment, the kits of the present invention contain a substantially isolated polypeptide comprising an epitope which is specifically immunoreactive with an antibody included in the kit. Preferably, the kits of the present invention further comprise a control antibody which does not react with the polypeptide of interest. In another specific embodiment, the kits of the present invention contain a means for detecting the binding of an antibody to a polypeptide of interest (e.g., the antibody may be conjugated to a detectable substrate such as a fluorescent compound, an enzymatic substrate, a radioactive compound or a luminescent compound, or a second antibody which recognizes the first antibody may be conjugated to a detectable substrate).



In another specific embodiment of the present invention, the kit is a diagnostic kit for use in screening serum containing antibodies specific against proliferative and/or cancerous polynucleotides and polypeptides. Such a kit may include a control antibody that does not react with the polypeptide of interest. Such a kit may include a  
5 substantially isolated polypeptide antigen comprising an epitope which is specifically immunoreactive with at least one anti-polypeptide antigen antibody. Further, such a kit includes means for detecting the binding of said antibody to the antigen (e.g., the antibody may be conjugated to a fluorescent compound such as fluorescein or rhodamine which can be detected by flow cytometry). In specific embodiments, the  
10 kit may include a recombinantly produced or chemically synthesized polypeptide antigen. The polypeptide antigen of the kit may also be attached to a solid support.

In a more specific embodiment the detecting means of the above-described kit includes a solid support to which said polypeptide antigen is attached. Such a kit may also include a non-attached reporter-labeled anti-human antibody. In this  
15 embodiment, binding of the antibody to the polypeptide antigen can be detected by binding of the said reporter-labeled antibody.

In an additional embodiment, the invention includes a diagnostic kit for use in screening serum containing antigens of the polypeptide of the invention. The diagnostic kit includes a substantially isolated antibody specifically immunoreactive  
20 with polypeptide or polynucleotide antigens, and means for detecting the binding of the polynucleotide or polypeptide antigen to the antibody. In one embodiment, the antibody is attached to a solid support. In a specific embodiment, the antibody may be a monoclonal antibody. The detecting means of the kit may include a second, labeled monoclonal antibody. Alternatively, or in addition, the detecting means may include  
25 a labeled, competing antigen.

In one diagnostic configuration, test serum is reacted with a solid phase reagent having a surface-bound antigen obtained by the methods of the present invention. After binding with specific antigen antibody to the reagent and removing unbound serum components by washing, the reagent is reacted with reporter-labeled  
30 anti-human antibody to bind reporter to the reagent in proportion to the amount of

bound anti-antigen antibody on the solid support. The reagent is again washed to remove unbound labeled antibody, and the amount of reporter associated with the reagent is determined. Typically, the reporter is an enzyme which is detected by incubating the solid phase in the presence of a suitable fluorometric, luminescent or colorimetric substrate (Sigma, St. Louis, MO).

The solid surface reagent in the above assay is prepared by known techniques for attaching protein material to solid support material, such as polymeric beads, dip sticks, 96-well plate or filter material. These attachment methods generally include non-specific adsorption of the protein to the support or covalent attachment of the protein, typically through a free amine group, to a chemically reactive group on the solid support, such as an activated carboxyl, hydroxyl, or aldehyde group. Alternatively, streptavidin coated plates can be used in conjunction with biotinylated antigen(s).

Thus, the invention provides an assay system or kit for carrying out this diagnostic method. The kit generally includes a support with surface-bound recombinant antigens, and a reporter-labeled anti-human antibody for detecting surface-bound anti-antigen antibody.

#### **Uses of the Polynucleotides**

Each of the polynucleotides identified herein can be used in numerous ways as reagents. The following description should be considered exemplary and utilizes known techniques.

The cancer antigen polynucleotides of the present invention are useful for chromosome identification. There exists an ongoing need to identify new chromosome markers, since few chromosome marking reagents, based on actual sequence data (repeat polymorphisms), are presently available. Each sequence is specifically targeted to and can hybridize with a particular location on an individual human chromosome, thus each polynucleotide of the present invention can routinely be used as a chromosome marker using techniques known in the art.

Briefly, sequences can be mapped to chromosomes by preparing PCR primers (preferably at least 15 bp (e.g., 15-25 bp) from the sequences shown in SEQ ID NO:X, or the complement thereto. Primers can optionally be selected using computer analysis so that primers do not span more than one predicted exon in the genomic DNA. These primers are then used for PCR screening of somatic cell hybrids containing individual human chromosomes. Only those hybrids containing the human gene corresponding to SEQ ID NO:X will yield an amplified fragment.

Similarly, somatic hybrids provide a rapid method of PCR mapping the polynucleotides to particular chromosomes. Three or more clones can be assigned per day using a single thermal cycler. Moreover, sublocalization of the polynucleotides can be achieved with panels of specific chromosome fragments. Other gene mapping strategies that can be used include in situ hybridization, prescreening with labeled flow-sorted chromosomes, preselection by hybridization to construct chromosome specific-cDNA libraries, and computer mapping techniques (See, e.g., Shuler, Trends Biotechnol 16:456-459 (1998) which is hereby incorporated by reference in its entirety).

Precise chromosomal location of the polynucleotides can also be achieved using fluorescence in situ hybridization (FISH) of a metaphase chromosomal spread. This technique uses polynucleotides as short as 500 or 600 bases; however, polynucleotides 2,000-4,000 bp are preferred. For a review of this technique, see Verma et al., "Human Chromosomes: a Manual of Basic Techniques," Pergamon Press, New York (1988).

For chromosome mapping, the polynucleotides can be used individually (to mark a single chromosome or a single site on that chromosome) or in panels (for marking multiple sites and/or multiple chromosomes).

Thus, the present invention also provides a method for chromosomal localization which involves (a) preparing PCR primers from the polynucleotide sequences in Table 3 and SEQ ID NO:X and (b) screening somatic cell hybrids containing individual chromosomes.

The polynucleotides of the present invention would likewise be useful for radiation hybrid mapping, HAPPY mapping, and long range restriction mapping. For a review of these techniques and others known in the art, see, e.g. Dear, "Genome Mapping: A Practical Approach," IRL Press at Oxford University Press, London (1997); Aydin, J. Mol. Med. 77:691-694 (1999); Hacia et al., Mol. Psychiatry 3:483-492 (1998); Herrick et al., Chromosome Res. 7:409-423 (1999); Hamilton et al., Methods Cell Biol. 62:265-280 (2000); and/or Ott, J. Hered. 90:68-70 (1999) each of which is hereby incorporated by reference in its entirety.

Once a polynucleotide has been mapped to a precise chromosomal location, the physical position of the polynucleotide can be used in linkage analysis. Linkage analysis establishes coinheritance between a chromosomal location and presentation of a particular disease. (Disease mapping data are found, for example, in V. McKusick, Mendelian Inheritance in Man (available on line through Johns Hopkins University Welch Medical Library).) Assuming 1 megabase mapping resolution and one gene per 20 kb, a cDNA precisely localized to a chromosomal region associated with the disease could be one of 50-500 potential causative genes.

Thus, once coinheritance is established, differences in a polynucleotide of the invention and the corresponding gene between affected and unaffected individuals can be examined. First, visible structural alterations in the chromosomes, such as deletions or translocations, are examined in chromosome spreads or by PCR. If no structural alterations exist, the presence of point mutations are ascertained. Mutations observed in some or all affected individuals, but not in normal individuals, indicates that the mutation may cause the disease. However, complete sequencing of the polypeptide and the corresponding gene from several normal individuals is required to distinguish the mutation from a polymorphism. If a new polymorphism is identified, this polymorphic polypeptide can be used for further linkage analysis.

Furthermore, increased or decreased expression of the gene in affected individuals as compared to unaffected individuals can be assessed using the polynucleotides of the invention. Any of these alterations (altered expression,

chromosomal rearrangement, or mutation) can be used as a diagnostic or prognostic marker.

Thus, the invention provides a method of detecting increased or decreased expression levels of the cancer polynucleotides in affected individuals as compared to  
5 unaffected individuals using polynucleotides of the present invention and techniques known in the art, including but not limited to the method described in Example 11. Any of these alterations (altered expression, chromosomal rearrangement, or mutation) can be used as a diagnostic or prognostic marker.

Thus, the invention also provides a diagnostic method useful during diagnosis  
10 of a tissue specific disorder, including cancer, involving measuring the expression level of cancer polynucleotides in tissues or other cells or body fluid from an individual and comparing the measured gene expression level with a standard cancer polynucleotide expression level, whereby an increase or decrease in the gene expression level compared to the standard is indicative of a tissue specific disorder.

15 In still another embodiment, the invention includes a kit for analyzing samples for the presence of proliferative and/or cancerous polynucleotides derived from a test subject. In a general embodiment, the kit includes at least one polynucleotide probe containing a nucleotide sequence that will specifically hybridize with a polynucleotide of the invention and a suitable container. In a specific embodiment,  
20 the kit includes two polynucleotide probes defining an internal region of the polynucleotide of the invention, where each probe has one strand containing a 31'-mer-end internal to the region. In a further embodiment, the probes may be useful as primers for polymerase chain reaction amplification.

Where a diagnosis of a tissue specific disorder, including, for example,  
25 diagnosis of a tumor, has already been made according to conventional methods, the present invention is useful as a prognostic indicator, whereby patients exhibiting enhanced or depressed cancer polynucleotide expression will experience a worse clinical outcome relative to patients expressing the gene at a level nearer the standard level.

By "measuring the expression level of cancer polynucleotides" is intended qualitatively or quantitatively measuring or estimating the level of the cancer polypeptide or the level of the mRNA encoding the cancer polypeptide in a first biological sample either directly (e.g., by determining or estimating absolute protein  
5 level or mRNA level) or relatively (e.g., by comparing to the cancer polypeptide level or mRNA level in a second biological sample). Preferably, the cancer polypeptide level or mRNA level in the first biological sample is measured or estimated and compared to a standard cancer polypeptide level or mRNA level, the standard being taken from a second biological sample obtained from an individual not having the  
10 tissue specific disorder or being determined by averaging levels from a population of individuals not having the tissue specific disorder. As will be appreciated in the art, once a standard cancer polypeptide level or mRNA level is known, it can be used repeatedly as a standard for comparison.

By "biological sample" is intended any biological sample obtained from an  
15 individual, body fluid, cell line, tissue culture, or other source which contains a cancer polypeptide or the corresponding mRNA. As indicated, biological samples include body fluids (such as sputum, breast milk, vaginal pool, bile, semen, lymph, sera, plasma, urine, synovial fluid and spinal fluid) which contain the cancer polypeptide, and other tissue sources found to express the cancer polypeptide. Methods for  
20 obtaining tissue biopsies and body fluids from mammals are well known in the art. Where the biological sample is to include mRNA, a tissue biopsy is the preferred source.

The method(s) provided above may preferably be applied in a diagnostic method and/or kits in which polynucleotides and/or polypeptides of the invention are  
25 attached to a solid support. In one exemplary method, the support may be a "gene chip" or a "biological chip" as described in US Patents 5,837,832, 5,874,219, and 5,856,174. Further, such a gene chip with cancer antigen polynucleotides attached may be used to identify polymorphisms between the cancer antigen polynucleotide sequences, with polynucleotides isolated from a test subject. The knowledge of such  
30 polymorphisms (i.e. their location, as well as, their existence) would be beneficial in

identifying disease loci for many disorders, such as for example, in neural disorders, immune system disorders, muscular disorders, reproductive disorders, gastrointestinal disorders, pulmonary disorders, cardiovascular disorders, renal disorders, proliferative disorders, and/or cancerous diseases and conditions. Such a method is described in  
5 US Patents 5,858,659 and 5,856,104. The US Patents referenced supra are hereby incorporated by reference in their entirety herein.

The present invention encompasses cancer polynucleotides that are chemically synthesized, or reproduced as peptide nucleic acids (PNA), or according to other methods known in the art. The use of PNAs would serve as the preferred form if the  
10 polynucleotides of the invention are incorporated onto a solid support, or gene chip. For the purposes of the present invention, a peptide nucleic acid (PNA) is a polyamide type of DNA analog and the monomeric units for adenine, guanine, thymine and cytosine are available commercially (Perceptive Biosystems). Certain components of DNA, such as phosphorus, phosphorus oxides, or deoxyribose  
15 derivatives, are not present in PNAs. As disclosed by P. E. Nielsen, M. Egholm, R. H. Berg and O. Buchardt, Science 254, 1497 (1991); and M. Egholm, O. Buchardt, L. Christensen, C. Behrens, S. M. Freier, D. A. Driver, R. H. Berg, S. K. Kim, B. Norden, and P. E. Nielsen, Nature 365, 666 (1993), PNAs bind specifically and tightly to complementary DNA strands and are not degraded by nucleases. In fact,  
20 PNA binds more strongly to DNA than DNA itself does. This is probably because there is no electrostatic repulsion between the two strands, and also the polyamide backbone is more flexible. Because of this, PNA/DNA duplexes bind under a wider range of stringency conditions than DNA/DNA duplexes, making it easier to perform multiplex hybridization. Smaller probes can be used than with DNA due to the strong  
25 binding. In addition, it is more likely that single base mismatches can be determined with PNA/DNA hybridization because a single mismatch in a PNA/DNA 15-mer lowers the melting point ( $T_{sub.m}$ ) by 8°-20° C, vs. 4°-16° C for the DNA/DNA 15-mer duplex. Also, the absence of charge groups in PNA means that hybridization can be done at low ionic strengths and reduce possible interference by salt during the  
30 analysis.

The present invention have uses which include, but are not limited to, detecting cancer in mammals. In particular the invention is useful during diagnosis of pathological cell proliferative neoplasias which include, but are not limited to: acute myelogenous leukemias including acute monocytic leukemia, acute myeloblastic leukemia, acute promyelocytic leukemia, acute myelomonocytic leukemia, acute erythroleukemia, acute megakaryocytic leukemia, and acute undifferentiated leukemia, etc.; and chronic myelogenous leukemias including chronic myelomonocytic leukemia, chronic granulocytic leukemia, etc. Preferred mammals include monkeys, apes, cats, dogs, cows, pigs, horses, rabbits and humans. Particularly preferred are humans.

Pathological cell proliferative disorders are often associated with inappropriate activation of proto-oncogenes. (Germann, E. P. et al., "The Etiology of Acute Leukemia: Molecular Genetics and Viral Oncology," in *Neoplastic Diseases of the Blood*, Vol 1., Wiernik, P. H. et al. eds., 161-182 (1985)). Neoplasias are now believed to result from the qualitative alteration of a normal cellular gene product, or from the quantitative modification of gene expression by insertion into the chromosome of a viral sequence, by chromosomal translocation of a gene to a more actively transcribed region, or by some other mechanism. (Germann et al., *supra*) It is likely that mutated or altered expression of specific genes is involved in the pathogenesis of some leukemias, among other tissues and cell types. (Germann et al., *supra*) Indeed, the human counterparts of the oncogenes involved in some animal neoplasias have been amplified or translocated in some cases of human leukemia and carcinoma. (Germann et al., *supra*)

For example, c-myc expression is highly amplified in the non-lymphocytic leukemia cell line HL-60. When HL-60 cells are chemically induced to stop proliferation, the level of c-myc is found to be downregulated. (International Publication Number WO 91/15580). However, it has been shown that exposure of HL-60 cells to a DNA construct that is complementary to the 5' end of c-myc or c-myb blocks translation of the corresponding mRNAs which downregulates expression of the c-myc or c-myb proteins and causes arrest of cell proliferation and



differentiation of the treated cells. (International Publication Number WO 91/15580; Wickstrom et al., Proc. Natl. Acad. Sci. 85:1028 (1988); Anfossi et al., Proc. Natl. Acad. Sci. 86:3379 (1989)). However, the skilled artisan would appreciate the present invention's usefulness is not limited to treatment of proliferative disorders of  
5 hematopoietic cells and tissues, in light of the numerous cells and cell types of varying origins which are known to exhibit proliferative phenotypes.

In addition to the foregoing, a cancer antigen polynucleotide can be used to control gene expression through triple helix formation or through antisense DNA or RNA. Antisense techniques are discussed, for example, in Okano, J. Neurochem. 56:  
10 560 (1991); "Oligodeoxynucleotides as Antisense Inhibitors of Gene Expression, CRC Press, Boca Raton, FL (1988). Triple helix formation is discussed in, for instance Lee et al., Nucleic Acids Research 6: 3073 (1979); Cooney et al., Science 241: 456 (1988); and Dervan et al., Science 251: 1360 (1991). Both methods rely on binding of the polynucleotide to a complementary DNA or RNA. For these  
15 techniques, preferred polynucleotides are usually oligonucleotides 20 to 40 bases in length and complementary to either the region of the gene involved in transcription (triple helix - see Lee et al., Nucl. Acids Res. 6:3073 (1979); Cooney et al., Science 241:456 (1988); and Dervan et al., Science 251:1360 (1991) ) or to the mRNA itself (antisense - Okano, J. Neurochem. 56:560 (1991); Oligodeoxy-nucleotides as  
20 Antisense Inhibitors of Gene Expression, CRC Press, Boca Raton, FL (1988).) Triple helix formation optimally results in a shut-off of RNA transcription from DNA, while antisense RNA hybridization blocks translation of an mRNA molecule into polypeptide. The oligonucleotide described above can also be delivered to cells such that the antisense RNA or DNA may be expressed in vivo to inhibit production of  
25 polypeptide of the present invention antigens. Both techniques are effective in model systems, and the information disclosed herein can be used to design antisense or triple helix polynucleotides in an effort to treat disease, and in particular, for the treatment of proliferative diseases and/or conditions.

Polynucleotides of the present invention are also useful in gene therapy. One  
30 goal of gene therapy is to insert a normal gene into an organism having a defective

gene, in an effort to correct the genetic defect. The polynucleotides disclosed in the present invention offer a means of targeting such genetic defects in a highly accurate manner. Another goal is to insert a new gene that was not present in the host genome, thereby producing a new trait in the host cell.

5       The polynucleotides are also useful for identifying individuals from minute biological samples. The United States military, for example, is considering the use of restriction fragment length polymorphism (RFLP) for identification of its personnel. In this technique, an individual's genomic DNA is digested with one or more restriction enzymes, and probed on a Southern blot to yield unique bands for  
10 identifying personnel. This method does not suffer from the current limitations of "Dog Tags" which can be lost, switched, or stolen, making positive identification difficult. The polynucleotides of the present invention can be used as additional DNA markers for RFLP.

      The polynucleotides of the present invention can also be used as an alternative  
15 to RFLP, by determining the actual base-by-base DNA sequence of selected portions of an individual's genome. These sequences can be used to prepare PCR primers for amplifying and isolating such selected DNA, which can then be sequenced. Using this technique, individuals can be identified because each individual will have a unique set of DNA sequences. Once an unique ID database is established for an  
20 individual, positive identification of that individual, living or dead, can be made from extremely small tissue samples.

      Forensic biology also benefits from using DNA-based identification techniques as disclosed herein. DNA sequences taken from very small biological samples such as tissues, e.g., hair or skin, or body fluids, e.g., blood, saliva, semen,  
25 synovial fluid, amniotic fluid, breast milk, lymph, pulmonary sputum or surfactant, urine, fecal matter, etc., can be amplified using PCR. In one prior art technique, gene sequences amplified from polymorphic loci, such as DQa class II HLA gene, are used in forensic biology to identify individuals. (Erlich, H., PCR Technology, Freeman and Co. (1992).) Once these specific polymorphic loci are amplified, they are  
30 digested with one or more restriction enzymes, yielding an identifying set of bands on

a Southern blot probed with DNA corresponding to the DQa class II HLA gene. Similarly, polynucleotides of the present invention can be used as polymorphic markers for forensic purposes.

5 There is also a need for reagents capable of identifying the source of a particular tissue. Such need arises, for example, in forensics when presented with tissue of unknown origin. Appropriate reagents can comprise, for example, DNA probes or primers specific to cancer polynucleotides prepared from the sequences of the present invention. Panels of such reagents can identify tissue by species and/or by organ type. In a similar fashion, these reagents can be used to screen tissue cultures  
10 for contamination.

The polynucleotides of the present invention are also useful as hybridization probes for differential identification of the tissue(s) or cell type(s) present in a biological sample. Similarly, polypeptides and antibodies directed to polypeptides of the present invention are useful to provide immunological probes for differential  
15 identification of the tissue(s) (e.g., immunohistochemistry assays) or cell type(s) (e.g., immunocytochemistry assays). In addition, for a number of disorders of the above tissues or cells, significantly higher or lower levels of gene expression of the polynucleotides/polypeptides of the present invention may be detected in certain tissues (e.g., tissues expressing polypeptides and/or polynucleotides of the present  
20 invention, cancer tissues and/or cancerous and/or wounded tissues) or bodily fluids (e.g., semen, vaginal pool, breast milk, bile, lymph, serum, plasma, urine, synovial fluid or spinal fluid) taken from an individual having such a disorder, relative to a "standard" gene expression level, i.e., the expression level in healthy tissue from an individual not having the disorder.

25 Thus, the invention provides a diagnostic method of a disorder, which involves: (a) assaying gene expression level in cells or body fluid of an individual; (b) comparing the gene expression level with a standard gene expression level, whereby an increase or decrease in the assayed gene expression level compared to the standard expression level is indicative of a disorder.

In the very least, the polynucleotides of the present invention can be used as molecular weight markers on Southern gels, as diagnostic probes for the presence of a specific mRNA in a particular cell type, as a probe to "subtract-out" known sequences in the process of discovering novel polynucleotides, for selecting and making oligomers for attachment to a "gene chip" or other support, to raise anti-DNA antibodies using DNA immunization techniques, and as an antigen to elicit an immune response.

#### **Uses of the Polypeptides**

Each of the polypeptides identified herein can be used in numerous ways. The following description should be considered exemplary and utilizes known techniques.

Polypeptides and antibodies directed to polypeptides of the present invention are useful to provide immunological probes for differential identification of the tissue(s) (e.g., immunohistochemistry assays such as, for example, ABC immunoperoxidase (Hsu et al., *J. Histochem. Cytochem.* 29:577-580 (1981)) or cell type(s) (e.g., immunocytochemistry assays).

Antibodies can be used to assay levels of polypeptides encoded by polynucleotides of the invention in a biological sample using classical immunohistological methods known to those of skill in the art (e.g., see Jalkanen, et al., *J. Cell. Biol.* 101:976-985 (1985); Jalkanen, et al., *J. Cell. Biol.* 105:3087-3096 (1987)). Other antibody-based methods useful for detecting protein gene expression include immunoassays, such as the enzyme linked immunosorbent assay (ELISA) and the radioimmunoassay (RIA). Suitable antibody assay labels are known in the art and include enzyme labels, such as, glucose oxidase; radioisotopes, such as iodine ( $^{131}\text{I}$ ,  $^{125}\text{I}$ ,  $^{123}\text{I}$ ,  $^{121}\text{I}$ ), carbon ( $^{14}\text{C}$ ), sulfur ( $^{35}\text{S}$ ), tritium ( $^3\text{H}$ ), indium ( $^{115\text{m}}\text{In}$ ,  $^{113\text{m}}\text{In}$ ,  $^{112}\text{In}$ ,  $^{111}\text{In}$ ), and technetium ( $^{99}\text{Tc}$ ,  $^{99\text{m}}\text{Tc}$ ), thallium ( $^{201}\text{Tl}$ ), gallium ( $^{68}\text{Ga}$ ,  $^{67}\text{Ga}$ ), palladium ( $^{103}\text{Pd}$ ), molybdenum ( $^{99}\text{Mo}$ ), xenon ( $^{133}\text{Xe}$ ), fluorine ( $^{18}\text{F}$ ),  $^{153}\text{Sm}$ ,  $^{177}\text{Lu}$ ,  $^{159}\text{Gd}$ ,  $^{149}\text{Pm}$ ,  $^{140}\text{La}$ ,  $^{175}\text{Yb}$ ,  $^{166}\text{Ho}$ ,  $^{90}\text{Y}$ ,  $^{47}\text{Sc}$ ,  $^{186}\text{Re}$ ,  $^{188}\text{Re}$ ,  $^{142}\text{Pr}$ ,  $^{105}\text{Rh}$ ,  $^{97}\text{Ru}$ ; luminescent labels, such as luminol; and fluorescent labels, such as fluorescein and rhodamine, and biotin.

In addition to assaying levels of polypeptide of the present invention in a biological sample, proteins can also be detected in vivo by imaging. Antibody labels or markers for in vivo imaging of protein include those detectable by X-radiography, NMR or ESR. For X-radiography, suitable labels include radioisotopes such as  
5 barium or cesium, which emit detectable radiation but are not overtly harmful to the subject. Suitable markers for NMR and ESR include those with a detectable characteristic spin, such as deuterium, which may be incorporated into the antibody by labeling of nutrients for the relevant hybridoma.

A protein-specific antibody or antibody fragment which has been labeled with  
10 an appropriate detectable imaging moiety, such as a radioisotope (for example,  $^{131}\text{I}$ ,  $^{112}\text{In}$ ,  $^{99\text{m}}\text{Tc}$ , ( $^{131}\text{I}$ ,  $^{125}\text{I}$ ,  $^{123}\text{I}$ ,  $^{121}\text{I}$ ), carbon ( $^{14}\text{C}$ ), sulfur ( $^{35}\text{S}$ ), tritium ( $^3\text{H}$ ), indium ( $^{115\text{m}}\text{In}$ ,  $^{113\text{m}}\text{In}$ ,  $^{112}\text{In}$ ,  $^{111}\text{In}$ ), and technetium ( $^{99}\text{Tc}$ ,  $^{99\text{m}}\text{Tc}$ ), thallium ( $^{201}\text{Tl}$ ), gallium ( $^{68}\text{Ga}$ ,  $^{67}\text{Ga}$ ), palladium ( $^{103}\text{Pd}$ ), molybdenum ( $^{99}\text{Mo}$ ), xenon ( $^{133}\text{Xe}$ ), fluorine ( $^{18}\text{F}$ ,  $^{153}\text{Sm}$ ,  $^{177}\text{Lu}$ ,  $^{159}\text{Gd}$ ,  $^{149}\text{Pm}$ ,  $^{140}\text{La}$ ,  $^{175}\text{Yb}$ ,  $^{166}\text{Ho}$ ,  $^{90}\text{Y}$ ,  $^{47}\text{Sc}$ ,  $^{186}\text{Re}$ ,  $^{188}\text{Re}$ ,  $^{142}\text{Pr}$ ,  $^{105}\text{Rh}$ ,  
15  $^{97}\text{Ru}$ ), a radio-opaque substance, or a material detectable by nuclear magnetic resonance, is introduced (for example, parenterally, subcutaneously or intraperitoneally) into the mammal to be examined for immune system disorder. It will be understood in the art that the size of the subject and the imaging system used will determine the quantity of imaging moiety needed to produce diagnostic images.  
20 In the case of a radioisotope moiety, for a human subject, the quantity of radioactivity injected will normally range from about 5 to 20 millicuries of  $^{99\text{m}}\text{Tc}$ . The labeled antibody or antibody fragment will then preferentially accumulate at the location of cells which express the polypeptide encoded by a polynucleotide of the invention. *In vivo* tumor imaging is described in S.W. Burchiel et al., "Immunopharmacokinetics of Radiolabeled Antibodies and Their Fragments" (Chapter 13 in *Tumor Imaging: The Radiochemical Detection of Cancer*, S.W. Burchiel and B. A. Rhodes, eds., Masson Publishing Inc. (1982)).

In one embodiment, the invention provides a method for the specific delivery of compositions of the invention to cells by administering polypeptides of the  
30 invention (e.g., polypeptides encoded by polynucleotides of the invention and/or

antibodies) that are associated with heterologous polypeptides or nucleic acids. In one example, the invention provides a method for delivering a therapeutic protein into the targeted cell. In another example, the invention provides a method for delivering a single stranded nucleic acid (e.g., antisense or ribozymes) or double stranded  
5 nucleic acid (e.g., DNA that can integrate into the cell's genome or replicate episomally and that can be transcribed) into the targeted cell.

In another embodiment, the invention provides a method for the specific destruction of cells (e.g., the destruction of tumor cells) by administering polypeptides of the invention in association with toxins or cytotoxic prodrugs.

10 By "toxin" is meant one or more compounds that bind and activate endogenous cytotoxic effector systems, radioisotopes, holotoxins, modified toxins, catalytic subunits of toxins, or any molecules or enzymes not normally present in or on the surface of a cell that under defined conditions cause the cell's death. Toxins that may be used according to the methods of the invention include, but are not  
15 limited to, radioisotopes known in the art, compounds such as, for example, antibodies (or complement fixing containing portions thereof) that bind an inherent or induced endogenous cytotoxic effector system, thymidine kinase, endonuclease, RNase, alpha toxin, ricin, abrin, *Pseudomonas* exotoxin A, diphtheria toxin, saporin, momordin, gelonin, pokeweed antiviral protein, alpha-sarcin and cholera toxin.  
20 "Toxin" also includes a cytostatic or cytocidal agent, a therapeutic agent or a radioactive metal ion, e.g., alpha-emitters such as, for example, <sup>213</sup>Bi, or other radioisotopes such as, for example, <sup>103</sup>Pd, <sup>133</sup>Xe, <sup>131</sup>I, <sup>68</sup>Ge, <sup>57</sup>Co, <sup>65</sup>Zn, <sup>85</sup>Sr, <sup>32</sup>P, <sup>35</sup>S, <sup>90</sup>Y, <sup>153</sup>Sm, <sup>153</sup>Gd, <sup>169</sup>Yb, <sup>51</sup>Cr, <sup>54</sup>Mn, <sup>75</sup>Se, <sup>113</sup>Sn, <sup>90</sup>Yttrium, <sup>117</sup>Tin, <sup>186</sup>Rhenium, <sup>166</sup>Holmium, and <sup>188</sup>Rhenium; luminescent labels, such as luminol; and fluorescent  
25 labels, such as fluorescein and rhodamine, and biotin.

Techniques known in the art may be applied to label polypeptides of the invention (including antibodies). Such techniques include, but are not limited to, the use of bifunctional conjugating agents (see e.g., U.S. Patent Nos. 5,756,065; 5,714,631; 5,696,239; 5,652,361; 5,505,931; 5,489,425; 5,435,990; 5,428,139;

5,342,604; 5,274,119; 4,994,560; and 5,808,003; the contents of each of which are hereby incorporated by reference in its entirety).

Thus, the invention provides a diagnostic method of a disorder, which involves (a) assaying the expression level of a cancer polypeptide of the present invention in cells or body fluid of an individual; and (b) comparing the assayed polypeptide expression level with a standard polypeptide expression level, whereby an increase or decrease in the assayed polypeptide expression level compared to the standard expression level is indicative of a disorder. With respect to cancer, the presence of a relatively high amount of transcript in biopsied tissue from an individual may indicate a predisposition for the development of the disease, or may provide a means for detecting the disease prior to the appearance of actual clinical symptoms. A more definitive diagnosis of this type may allow health professionals to employ preventative measures or aggressive treatment earlier thereby preventing the development or further progression of the cancer.

Moreover, cancer antigen polypeptides of the present invention can be used to treat or prevent diseases or conditions such as, for example, neural disorders, immune system disorders, muscular disorders, reproductive disorders, gastrointestinal disorders, pulmonary disorders, cardiovascular disorders, renal disorders, proliferative disorders, and/or cancerous diseases and conditions. For example, patients can be administered a polypeptide of the present invention in an effort to replace absent or decreased levels of the polypeptide (e.g., insulin), to supplement absent or decreased levels of a different polypeptide (e.g., hemoglobin S for hemoglobin B, SOD, catalase, DNA repair proteins), to inhibit the activity of a polypeptide (e.g., an oncogene or tumor suppressor), to activate the activity of a polypeptide (e.g., by binding to a receptor), to reduce the activity of a membrane bound receptor by competing with it for free ligand (e.g., soluble TNF receptors used in reducing inflammation), or to bring about a desired response (e.g., blood vessel growth inhibition, enhancement of the immune response to proliferative cells or tissues).

Similarly, antibodies directed to a polypeptide of the present invention can also be used to treat disease (as described supra, and elsewhere herein). For example,

administration of an antibody directed to a polypeptide of the present invention can bind, and/or neutralize the polypeptide, and/or reduce overproduction of the polypeptide. Similarly, administration of an antibody can activate the polypeptide, such as by binding to a polypeptide bound to a membrane (receptor).

5           At the very least, the polypeptides of the present invention can be used as molecular weight markers on SDS-PAGE gels or on molecular sieve gel filtration columns using methods well known to those of skill in the art. Polypeptides can also be used to raise antibodies, which in turn are used to measure protein expression from a recombinant cell, as a way of assessing transformation of the host cell. Moreover,  
10           the polypeptides of the present invention can be used to test the following biological activities.

#### **Gene Therapy Methods**

          Another aspect of the present invention is to gene therapy methods for treating  
15           or preventing disorders, diseases and conditions. The gene therapy methods relate to the introduction of nucleic acid (DNA, RNA and antisense DNA or RNA) sequences into an animal to achieve expression of the polypeptide of the present invention. This method requires a polynucleotide which codes for a polypeptide of the present invention operatively linked to a promoter and any other genetic elements necessary  
20           for the expression of the polypeptide by the target tissue. Such gene therapy and delivery techniques are known in the art, see, for example, WO90/11092, which is herein incorporated by reference.

          Thus, for example, cells from a patient may be engineered with a polynucleotide (DNA or RNA) comprising a promoter operably linked to a  
25           polynucleotide of the present invention ex vivo, with the engineered cells then being provided to a patient to be treated with the polypeptide of the present invention. Such methods are well-known in the art. For example, see Beldegrun, A., et al., J. Natl. Cancer Inst. 85: 207-216 (1993); Ferrantini, M. et al., Cancer Research 53: 1107-1112 (1993); Ferrantini, M. et al., J. Immunology 153: 4604-4615 (1994); Kaido, T., et al.,  
30           Int. J. Cancer 60: 221-229 (1995); Ogura, H., et al., Cancer Research 50: 5102-5106



(1990); Santodonato, L., et al., Human Gene Therapy 7:1-10 (1996); Santodonato, L., et al., Gene Therapy 4:1246-1255 (1997); and Zhang, J.-F. et al., Cancer Gene Therapy 3: 31-38 (1996)), which are herein incorporated by reference. In one embodiment, the cells which are engineered are arterial cells. The arterial cells may  
5 be reintroduced into the patient through direct injection to the artery, the tissues surrounding the artery, or through catheter injection.

As discussed in more detail below, the polynucleotide constructs can be delivered by any method that delivers injectable materials to the cells of an animal, such as, injection into the interstitial space of tissues (heart, muscle, skin, lung, liver,  
10 and the like). The polynucleotide constructs may be delivered in a pharmaceutically acceptable liquid or aqueous carrier.

In one embodiment, the polynucleotide of the present invention is delivered as a naked polynucleotide. The term "naked" polynucleotide, DNA or RNA refers to sequences that are free from any delivery vehicle that acts to assist, promote or  
15 facilitate entry into the cell, including viral sequences, viral particles, liposome formulations, lipofectin or precipitating agents and the like. However, the polynucleotide of the present invention can also be delivered in liposome formulations and lipofectin formulations and the like can be prepared by methods well known to those skilled in the art. Such methods are described, for example, in  
20 U.S. Patent Nos. 5,593,972, 5,589,466, and 5,580,859, which are herein incorporated by reference.

The polynucleotide vector constructs used in the gene therapy method are preferably constructs that will not integrate into the host genome nor will they contain sequences that allow for replication. Appropriate vectors include pWLNEO,  
25 pSV2CAT, pOG44, pXT1 and pSG available from Stratagene; pSVK3, pBPV, pMSG and pSVL available from Pharmacia; and pEF1/V5, pcDNA3.1, and pRc/CMV2 available from Invitrogen. Other suitable vectors will be readily apparent to the skilled artisan.

Any strong promoter known to those skilled in the art can be used for driving  
30 the expression of the polynucleotide sequence. Suitable promoters include adenoviral

promoters, such as the adenoviral major late promoter; or heterologous promoters, such as the cytomegalovirus (CMV) promoter; the respiratory syncytial virus (RSV) promoter; inducible promoters, such as the MMT promoter, the metallothionein promoter; heat shock promoters; the albumin promoter; the ApoA1 promoter; human  
5 globin promoters; viral thymidine kinase promoters, such as the Herpes Simplex thymidine kinase promoter; retroviral LTRs; the b-actin promoter; and human growth hormone promoters. The promoter also may be the native promoter for the polynucleotide of the present invention.

Unlike other gene therapy techniques, one major advantage of introducing  
10 naked nucleic acid sequences into target cells is the transitory nature of the polynucleotide synthesis in the cells. Studies have shown that non-replicating DNA sequences can be introduced into cells to provide production of the desired polypeptide for periods of up to six months.

The polynucleotide construct can be delivered to the interstitial space of tissues  
15 within the an animal, including of muscle, skin, brain, lung, liver, spleen, bone marrow, thymus, heart, lymph, blood, bone, cartilage, pancreas, kidney, gall bladder, stomach, intestine, testis, ovary, uterus, rectum, nervous system, eye, gland, and connective tissue. Interstitial space of the tissues comprises the intercellular, fluid, mucopolysaccharide matrix among the reticular fibers of organ tissues, elastic fibers in  
20 the walls of vessels or chambers, collagen fibers of fibrous tissues, or that same matrix within connective tissue ensheathing muscle cells or in the lacunae of bone. It is similarly the space occupied by the plasma of the circulation and the lymph fluid of the lymphatic channels. Delivery to the interstitial space of muscle tissue is preferred for the reasons discussed below. They may be conveniently delivered by injection into the  
25 tissues comprising these cells. They are preferably delivered to and expressed in persistent, non-dividing cells which are differentiated, although delivery and expression may be achieved in non-differentiated or less completely differentiated cells, such as, for example, stem cells of blood or skin fibroblasts. In vivo muscle cells are particularly competent in their ability to take up and express polynucleotides.

For the naked nucleic acid sequence injection, an effective dosage amount of DNA or RNA will be in the range of from about 0.05 mg/kg body weight to about 50 mg/kg body weight. Preferably the dosage will be from about 0.005 mg/kg to about 20 mg/kg and more preferably from about 0.05 mg/kg to about 5 mg/kg. Of course, as  
5 the artisan of ordinary skill will appreciate, this dosage will vary according to the tissue site of injection. The appropriate and effective dosage of nucleic acid sequence can readily be determined by those of ordinary skill in the art and may depend on the condition being treated and the route of administration.

The preferred route of administration is by the parenteral route of injection  
10 into the interstitial space of tissues. However, other parenteral routes may also be used, such as, inhalation of an aerosol formulation particularly for delivery to lungs or bronchial tissues, throat or mucous membranes of the nose. In addition, naked DNA constructs can be delivered to arteries during angioplasty by the catheter used in the procedure.

15 The naked polynucleotides are delivered by any method known in the art, including, but not limited to, direct needle injection at the delivery site, intravenous injection, topical administration, catheter infusion, and so-called "gene guns". These delivery methods are known in the art.

The constructs may also be delivered with delivery vehicles such as viral  
20 sequences, viral particles, liposome formulations, lipofectin, precipitating agents, etc. Such methods of delivery are known in the art.

In certain embodiments, the polynucleotide constructs are complexed in a liposome preparation. Liposomal preparations for use in the instant invention include cationic (positively charged), anionic (negatively charged) and neutral preparations.  
25 However, cationic liposomes are particularly preferred because a tight charge complex can be formed between the cationic liposome and the polyanionic nucleic acid. Cationic liposomes have been shown to mediate intracellular delivery of plasmid DNA (Felgner et al., Proc. Natl. Acad. Sci. USA (1987) 84:7413-7416, which is herein incorporated by reference); mRNA (Malone et al., Proc. Natl. Acad. Sci. USA  
30 (1989) 86:6077-6081, which is herein incorporated by reference); and purified

transcription factors (Debs et al., J. Biol. Chem. (1990) 265:10189-10192, which is herein incorporated by reference), in functional form.

Cationic liposomes are readily available. For example, N[1-2,3-dioleoyloxy)propyl]-N,N,N-triethylammonium (DOTMA) liposomes are particularly useful and are available under the trademark Lipofectin, from GIBCO BRL, Grand Island, N.Y. (See, also, Felgner et al., Proc. Natl Acad. Sci. USA (1987) 84:7413-7416, which is herein incorporated by reference). Other commercially available liposomes include transfectace (DDAB/DOPE) and DOTAP/DOPE (Boehringer).

Other cationic liposomes can be prepared from readily available materials using techniques well known in the art. See, e.g. PCT Publication No. WO 90/11092 (which is herein incorporated by reference) for a description of the synthesis of DOTAP (1,2-bis(oleoyloxy)-3-(trimethylammonio)propane) liposomes. Preparation of DOTMA liposomes is explained in the literature, see, e.g., P. Felgner et al., Proc. Natl. Acad. Sci. USA 84:7413-7417, which is herein incorporated by reference. Similar methods can be used to prepare liposomes from other cationic lipid materials.

Similarly, anionic and neutral liposomes are readily available, such as from Avanti Polar Lipids (Birmingham, Ala.), or can be easily prepared using readily available materials. Such materials include phosphatidyl, choline, cholesterol, phosphatidyl ethanolamine, dioleoylphosphatidyl choline (DOPC), dioleoylphosphatidyl glycerol (DOPG), dioleoylphosphatidyl ethanolamine (DOPE), among others. These materials can also be mixed with the DOTMA and DOTAP starting materials in appropriate ratios. Methods for making liposomes using these materials are well known in the art.

For example, commercially dioleoylphosphatidyl choline (DOPC), dioleoylphosphatidyl glycerol (DOPG), and dioleoylphosphatidyl ethanolamine (DOPE) can be used in various combinations to make conventional liposomes, with or without the addition of cholesterol. Thus, for example, DOPG/DOPC vesicles can be prepared by drying 50 mg each of DOPG and DOPC under a stream of nitrogen gas into a sonication vial. The sample is placed under a vacuum pump overnight and

is hydrated the following day with deionized water. The sample is then sonicated for 2 hours in a capped vial, using a Heat Systems model 350 sonicator equipped with an inverted cup (bath type) probe at the maximum setting while the bath is circulated at 15EC. Alternatively, negatively charged vesicles can be prepared without sonication  
5 to produce multilamellar vesicles or by extrusion through nucleopore membranes to produce unilamellar vesicles of discrete size. Other methods are known and available to those of skill in the art.

The liposomes can comprise multilamellar vesicles (MLVs), small unilamellar vesicles (SUVs), or large unilamellar vesicles (LUVs), with SUVs being preferred.  
10 The various liposome-nucleic acid complexes are prepared using methods well known in the art. See, e.g., Straubinger et al., *Methods of Immunology* (1983), 101:512-527, which is herein incorporated by reference. For example, MLVs containing nucleic acid can be prepared by depositing a thin film of phospholipid on the walls of a glass tube and subsequently hydrating with a solution of the material to be encapsulated.  
15 SUVs are prepared by extended sonication of MLVs to produce a homogeneous population of unilamellar liposomes. The material to be entrapped is added to a suspension of preformed MLVs and then sonicated. When using liposomes containing cationic lipids, the dried lipid film is resuspended in an appropriate solution such as sterile water or an isotonic buffer solution such as 10 mM Tris/NaCl, sonicated, and  
20 then the preformed liposomes are mixed directly with the DNA. The liposome and DNA form a very stable complex due to binding of the positively charged liposomes to the cationic DNA. SUVs find use with small nucleic acid fragments. LUVs are prepared by a number of methods, well known in the art. Commonly used methods include  $\text{Ca}^{2+}$ -EDTA chelation (Papahadjopoulos et al., *Biochim. Biophys. Acta*  
25 (1975) 394:483; Wilson et al., *Cell* (1979) 17:77); ether injection (Deamer, D. and Bangham, A., *Biochim. Biophys. Acta* (1976) 443:629; Ostro et al., *Biochem. Biophys. Res. Commun.* (1977) 76:836; Fraley et al., *Proc. Natl. Acad. Sci. USA* (1979) 76:3348); detergent dialysis (Enoch, H. and Strittmatter, P., *Proc. Natl. Acad. Sci. USA* (1979) 76:145); and reverse-phase evaporation (REV) (Fraley et al., *J. Biol.*  
30 *Chem.* (1980) 255:10431; Szoka, F. and Papahadjopoulos, D., *Proc. Natl. Acad. Sci.*

USA (1978) 75:145; Schaefer-Ridder et al., Science (1982) 215:166), which are herein incorporated by reference.

Generally, the ratio of DNA to liposomes will be from about 10:1 to about 1:10. Preferably, the ration will be from about 5:1 to about 1:5. More preferably, the  
5 ration will be about 3:1 to about 1:3. Still more preferably, the ratio will be about 1:1.

U.S. Patent No. 5,676,954 (which is herein incorporated by reference) reports on the injection of genetic material, complexed with cationic liposomes carriers, into mice. U.S. Patent Nos. 4,897,355, 4,946,787, 5,049,386, 5,459,127, 5,589,466, 5,693,622, 5,580,859, 5,703,055, and international publication no. WO 94/9469  
10 (which are herein incorporated by reference) provide cationic lipids for use in transfecting DNA into cells and mammals. U.S. Patent Nos. 5,589,466, 5,693,622, 5,580,859, 5,703,055, and international publication no. WO 94/9469 (which are herein incorporated by reference) provide methods for delivering DNA-cationic lipid complexes to mammals.

15 In certain embodiments, cells are engineered, ex vivo or in vivo, using a retroviral particle containing RNA which comprises a sequence encoding a polypeptide of the present invention. Retroviruses from which the retroviral plasmid vectors may be derived include, but are not limited to, Moloney Murine Leukemia Virus, spleen necrosis virus, Rous sarcoma Virus, Harvey Sarcoma Virus, avian  
20 leukosis virus, gibbon ape leukemia virus, human immunodeficiency virus, Myeloproliferative Sarcoma Virus, and mammary tumor virus.

The retroviral plasmid vector is employed to transduce packaging cell lines to form producer cell lines. Examples of packaging cells which may be transfected include, but are not limited to, the PE501, PA317, R-2, R-AM, PA12, T19-14X, VT-  
25 19-17-H2, RCRE, RCRIP, GP+E-86, GP+envAm12, and DAN cell lines as described in Miller, Human Gene Therapy 1:5-14 (1990), which is incorporated herein by reference in its entirety. The vector may transduce the packaging cells through any means known in the art. Such means include, but are not limited to, electroporation, the use of liposomes, and CaPO<sub>4</sub> precipitation. In one alternative, the retroviral

plasmid vector may be encapsulated into a liposome, or coupled to a lipid, and then administered to a host.

The producer cell line generates infectious retroviral vector particles which include polynucleotide encoding a polypeptide of the present invention. Such retroviral vector particles then may be employed, to transduce eukaryotic cells, either in vitro or in vivo. The transduced eukaryotic cells will express a polypeptide of the present invention.

In certain other embodiments, cells are engineered, ex vivo or in vivo, with polynucleotide contained in an adenovirus vector. Adenovirus can be manipulated such that it encodes and expresses a polypeptide of the present invention, and at the same time is inactivated in terms of its ability to replicate in a normal lytic viral life cycle. Adenovirus expression is achieved without integration of the viral DNA into the host cell chromosome, thereby alleviating concerns about insertional mutagenesis. Furthermore, adenoviruses have been used as live enteric vaccines for many years with an excellent safety profile (Schwartz, A. R. et al. (1974) *Am. Rev. Respir. Dis.* 109:233-238). Finally, adenovirus mediated gene transfer has been demonstrated in a number of instances including transfer of alpha-1-antitrypsin and CFTR to the lungs of cotton rats (Rosenfeld, M. A. et al. (1991) *Science* 252:431-434; Rosenfeld et al., (1992) *Cell* 68:143-155). Furthermore, extensive studies to attempt to establish adenovirus as a causative agent in human cancer were uniformly negative (Green, M. et al. (1979) *Proc. Natl. Acad. Sci. USA* 76:6606).

Suitable adenoviral vectors useful in the present invention are described, for example, in Kozarsky and Wilson, *Curr. Opin. Genet. Devel.* 3:499-503 (1993); Rosenfeld et al., *Cell* 68:143-155 (1992); Engelhardt et al., *Human Genet. Ther.* 4:759-769 (1993); Yang et al., *Nature Genet.* 7:362-369 (1994); Wilson et al., *Nature* 365:691-692 (1993); and U.S. Patent No. 5,652,224, which are herein incorporated by reference. For example, the adenovirus vector Ad2 is useful and can be grown in human 293 cells. These cells contain the E1 region of adenovirus and constitutively express Ela and Elb, which complement the defective adenoviruses by providing the

products of the genes deleted from the vector. In addition to Ad2, other varieties of adenovirus (e.g., Ad3, Ad5, and Ad7) are also useful in the present invention.

Preferably, the adenoviruses used in the present invention are replication deficient. Replication deficient adenoviruses require the aid of a helper virus and/or packaging cell line to form infectious particles. The resulting virus is capable of infecting cells and can express a polynucleotide of interest which is operably linked to a promoter, but cannot replicate in most cells. Replication deficient adenoviruses may be deleted in one or more of all or a portion of the following genes: E1a, E1b, E3, E4, E2a, or L1 through L5.

In certain other embodiments, the cells are engineered, ex vivo or in vivo, using an adeno-associated virus (AAV). AAVs are naturally occurring defective viruses that require helper viruses to produce infectious particles (Muzyczka, N., Curr. Topics in Microbiol. Immunol. 158:97 (1992)). It is also one of the few viruses that may integrate its DNA into non-dividing cells. Vectors containing as little as 300 base pairs of AAV can be packaged and can integrate, but space for exogenous DNA is limited to about 4.5 kb. Methods for producing and using such AAVs are known in the art. See, for example, U.S. Patent Nos. 5,139,941, 5,173,414, 5,354,678, 5,436,146, 5,474,935, 5,478,745, and 5,589,377.

For example, an appropriate AAV vector for use in the present invention will include all the sequences necessary for DNA replication, encapsidation, and host-cell integration. The polynucleotide construct is inserted into the AAV vector using standard cloning methods, such as those found in Sambrook et al., Molecular Cloning: A Laboratory Manual, Cold Spring Harbor Press (1989). The recombinant AAV vector is then transfected into packaging cells which are infected with a helper virus, using any standard technique, including lipofection, electroporation, calcium phosphate precipitation, etc. Appropriate helper viruses include adenoviruses, cytomegaloviruses, vaccinia viruses, or herpes viruses. Once the packaging cells are transfected and infected, they will produce infectious AAV viral particles which contain the polynucleotide construct. These viral particles are then used to transduce eukaryotic cells, either ex vivo or in vivo. The transduced cells will contain the



polynucleotide construct integrated into its genome, and will express a polypeptide of the invention.

Another method of gene therapy involves operably associating heterologous control regions and endogenous polynucleotide sequences (e.g. encoding a polypeptide of the present invention) via homologous recombination (see, e.g., U.S. Patent No. 5,641,670, issued June 24, 1997; International Publication No. WO 96/29411, published September 26, 1996; International Publication No. WO 94/12650, published August 4, 1994; Koller et al., Proc. Natl. Acad. Sci. USA 86:8932-8935 (1989); and Zijlstra et al., Nature 342:435-438 (1989). This method involves the activation of a gene which is present in the target cells, but which is not normally expressed in the cells, or is expressed at a lower level than desired.

Polynucleotide constructs are made, using standard techniques known in the art, which contain the promoter with targeting sequences flanking the promoter. Suitable promoters are described herein. The targeting sequence is sufficiently complementary to an endogenous sequence to permit homologous recombination of the promoter-targeting sequence with the endogenous sequence. The targeting sequence will be sufficiently near the 5' end of the desired endogenous polynucleotide sequence so the promoter will be operably linked to the endogenous sequence upon homologous recombination.

The promoter and the targeting sequences can be amplified using PCR. Preferably, the amplified promoter contains distinct restriction enzyme sites on the 5' and 3' ends. Preferably, the 3' end of the first targeting sequence contains the same restriction enzyme site as the 5' end of the amplified promoter and the 5' end of the second targeting sequence contains the same restriction site as the 3' end of the amplified promoter. The amplified promoter and targeting sequences are digested and ligated together.

The promoter-targeting sequence construct is delivered to the cells, either as naked polynucleotide, or in conjunction with transfection-facilitating agents, such as liposomes, viral sequences, viral particles, whole viruses, lipofection, precipitating agents, etc., described in more detail above. The P promoter-targeting sequence can

be delivered by any method, included direct needle injection, intravenous injection, topical administration, catheter infusion, particle accelerators, etc. The methods are described in more detail below.

5 The promoter-targeting sequence construct is taken up by cells. Homologous recombination between the construct and the endogenous sequence takes place, such that an endogenous sequence is placed under the control of the promoter. The promoter then drives the expression of the endogenous sequence.

10 Preferably, the polynucleotide encoding a polypeptide of the present invention contains a secretory signal sequence that facilitates secretion of the protein. Typically, the signal sequence is positioned in the coding region of the polynucleotide to be expressed towards or at the 5' end of the coding region. The signal sequence may be homologous or heterologous to the polynucleotide of interest and may be homologous or heterologous to the cells to be transfected. Additionally, the signal sequence may be chemically synthesized using methods known in the art.

15 Any mode of administration of any of the above-described polynucleotides constructs can be used so long as the mode results in the expression of one or more molecules in an amount sufficient to provide a therapeutic effect. This includes direct needle injection, systemic injection, catheter infusion, biolistic injectors, particle accelerators (i.e., "gene guns"), gelfoam sponge depots, other commercially available depot materials, osmotic pumps (e.g., Alza minipumps), oral or suppositorial solid (tablet or pill) pharmaceutical formulations, and decanting or topical applications during surgery. For example, direct injection of naked calcium phosphate-precipitated plasmid into rat liver and rat spleen or a protein-coated plasmid into the portal vein has resulted in gene expression of the foreign gene in the rat livers (Kaneda et al., Science 243:375 (1989)).

25 A preferred method of local administration is by direct injection. Preferably, a recombinant molecule of the present invention complexed with a delivery vehicle is administered by direct injection into or locally within the area of arteries. Administration of a composition locally within the area of arteries refers to injecting the composition centimeters and preferably, millimeters within arteries.

Another method of local administration is to contact a polynucleotide construct of the present invention in or around a surgical wound. For example, a patient can undergo surgery and the polynucleotide construct can be coated on the surface of tissue inside the wound or the construct can be injected into areas of tissue  
5 inside the wound.

Therapeutic compositions useful in systemic administration, include recombinant molecules of the present invention complexed to a targeted delivery vehicle of the present invention. Suitable delivery vehicles for use with systemic administration comprise liposomes comprising ligands for targeting the vehicle to a  
10 particular site.

Preferred methods of systemic administration, include intravenous injection, aerosol, oral and percutaneous (topical) delivery. Intravenous injections can be performed using methods standard in the art. Aerosol delivery can also be performed using methods standard in the art (see, for example, Stribling et al., Proc. Natl. Acad.  
15 Sci. USA 189:11277-11281, 1992, which is incorporated herein by reference). Oral delivery can be performed by complexing a polynucleotide construct of the present invention to a carrier capable of withstanding degradation by digestive enzymes in the gut of an animal. Examples of such carriers, include plastic capsules or tablets, such as those known in the art. Topical delivery can be performed by mixing a  
20 polynucleotide construct of the present invention with a lipophilic reagent (e.g., DMSO) that is capable of passing into the skin.

Determining an effective amount of substance to be delivered can depend upon a number of factors including, for example, the chemical structure and biological activity of the substance, the age and weight of the animal, the precise  
25 condition requiring treatment and its severity, and the route of administration. The frequency of treatments depends upon a number of factors, such as the amount of polynucleotide constructs administered per dose, as well as the health and history of the subject. The precise amount, number of doses, and timing of doses will be determined by the attending physician or veterinarian.

Therapeutic compositions of the present invention can be administered to any animal, preferably to mammals and birds. Preferred mammals include humans, dogs, cats, mice, rats, rabbits sheep, cattle, horses and pigs, with humans being particularly preferred.

5

#### **Biological Activities**

Polynucleotides or polypeptides, or agonists or antagonists of the present invention, can be used in assays to test for one or more biological activities. If these polynucleotides or polypeptides, or agonists or antagonists of the present invention, do exhibit activity in a particular assay, it is likely that these molecules may be involved in the diseases associated with the biological activity. Thus, the polynucleotides and polypeptides, and agonists or antagonists could be used to treat the associated disease.

15

#### **Immune Activity**

A polypeptide or polynucleotide, or agonists or antagonists of the present invention may be useful in treating deficiencies or disorders of the immune system, by activating or inhibiting the proliferation, differentiation, or mobilization (chemotaxis) of immune cells. Immune cells develop through a process called hematopoiesis, producing myeloid (platelets, red blood cells, neutrophils, and macrophages) and lymphoid (B and T lymphocytes) cells from pluripotent stem cells. The etiology of these immune deficiencies or disorders may be genetic, somatic, such as cancer or some autoimmune disorders, acquired (e.g., by chemotherapy or toxins), or infectious. Moreover, polynucleotides or polypeptides, or agonists or antagonists of the present invention can be used as a marker or detector of a particular immune system disease or disorder.

Polynucleotides or polypeptides, or agonists or antagonists of the present invention may be useful in treating or detecting deficiencies or disorders of hematopoietic cells. Polynucleotides or polypeptides, or agonists or antagonists of the present invention could be used to increase differentiation and proliferation of

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hematopoietic cells, including the pluripotent stem cells, in an effort to treat those disorders associated with a decrease in certain (or many) types hematopoietic cells. Examples of immunologic deficiency syndromes include, but are not limited to: blood protein disorders (e.g. agammaglobulinemia, dysgammaglobulinemia), ataxia  
5 telangiectasia, common variable immunodeficiency, Digeorge Syndrome, HIV infection, HTLV-BLV infection, leukocyte adhesion deficiency syndrome, lymphopenia, phagocyte bactericidal dysfunction, severe combined immunodeficiency (SCIDs), Wiskott-Aldrich Disorder, anemia, thrombocytopenia, or hemoglobinuria.

10 Moreover, polynucleotides or polypeptides, or agonists or antagonists of the present invention could also be used to modulate hemostatic (the stopping of bleeding) or thrombolytic activity (clot formation). For example, by increasing hemostatic or thrombolytic activity, polynucleotides or polypeptides, or agonists or antagonists of the present invention could be used to treat blood coagulation disorders  
15 (e.g., afibrinogenemia, factor deficiencies), blood platelet disorders (e.g. thrombocytopenia), or wounds resulting from trauma, surgery, or other causes. Alternatively, polynucleotides or polypeptides, or agonists or antagonists of the present invention that can decrease hemostatic or thrombolytic activity could be used to inhibit or dissolve clotting. These molecules could be important in the treatment of  
20 heart attacks (infarction), strokes, or scarring.

Polynucleotides or polypeptides, or agonists or antagonists of the present invention may also be useful in treating or detecting autoimmune disorders. Many autoimmune disorders result from inappropriate recognition of self as foreign material by immune cells. This inappropriate recognition results in an immune response  
25 leading to the destruction of the host tissue. Therefore, the administration of polynucleotides or polypeptides, or agonists or antagonists of the present invention that can inhibit an immune response, particularly the proliferation, differentiation, or chemotaxis of T-cells, may be an effective therapy in preventing autoimmune disorders.

Examples of autoimmune disorders that can be treated or detected include, but are not limited to: Addison's Disease, hemolytic anemia, antiphospholipid syndrome, rheumatoid arthritis, dermatitis, allergic encephalomyelitis, glomerulonephritis, Goodpasture's Syndrome, Graves' Disease, Multiple Sclerosis, Myasthenia Gravis, Neuritis, Ophthalmia, Bullous Pemphigoid, Pemphigus, Polyendocrinopathies, Purpura, Reiter's Disease, Stiff-Man Syndrome, Autoimmune Thyroiditis, Systemic Lupus Erythematosus, Autoimmune Pulmonary Inflammation, Guillain-Barre Syndrome, insulin dependent diabetes mellitus, and autoimmune inflammatory eye disease.

Similarly, allergic reactions and conditions, such as asthma (particularly allergic asthma) or other respiratory problems, may also be treated by polynucleotides or polypeptides, or agonists or antagonists of the present invention. Moreover, these molecules can be used to treat anaphylaxis, hypersensitivity to an antigenic molecule, or blood group incompatibility.

Polynucleotides or polypeptides, or agonists or antagonists of the present invention may also be used to treat and/or prevent organ rejection or graft-versus-host disease (GVHD). Organ rejection occurs by host immune cell destruction of the transplanted tissue through an immune response. Similarly, an immune response is also involved in GVHD, but, in this case, the foreign transplanted immune cells destroy the host tissues. The administration of polynucleotides or polypeptides, or agonists or antagonists of the present invention that inhibits an immune response, particularly the proliferation, differentiation, or chemotaxis of T-cells, may be an effective therapy in preventing organ rejection or GVHD.

Similarly, polynucleotides or polypeptides, or agonists or antagonists of the present invention may also be used to modulate inflammation. For example, polynucleotides or polypeptides, or agonists or antagonists of the present invention may inhibit the proliferation and differentiation of cells involved in an inflammatory response. These molecules can be used to treat inflammatory conditions, both chronic and acute conditions, including chronic prostatitis, granulomatous prostatitis and malacoplakia, inflammation associated with infection (e.g., septic shock, sepsis, or

systemic inflammatory response syndrome (SIRS)), ischemia-reperfusion injury, endotoxin lethality, arthritis, complement-mediated hyperacute rejection, nephritis, cytokine or chemokine induced lung injury, inflammatory bowel disease, Crohn's disease, or resulting from over production of cytokines (e.g., TNF or IL-1.)

5

#### **Hyperproliferative Disorders**

Polynucleotides or polypeptides, or agonists or antagonists of the present invention can be used to treat or detect hyperproliferative disorders, including neoplasms. Polynucleotides or polypeptides, or agonists or antagonists of the present  
10 invention may inhibit the proliferation of the disorder through direct or indirect interactions. Alternatively, Polynucleotides or polypeptides, or agonists or antagonists of the present invention may proliferate other cells which can inhibit the hyperproliferative disorder.

For example, by increasing an immune response, particularly increasing  
15 antigenic qualities of the hyperproliferative disorder or by proliferating, differentiating, or mobilizing T-cells, hyperproliferative disorders can be treated. This immune response may be increased by either enhancing an existing immune response, or by initiating a new immune response. Alternatively, decreasing an immune response may also be a method of treating hyperproliferative disorders, such  
20 as a chemotherapeutic agent.

Examples of hyperproliferative disorders that can be treated or detected by Polynucleotides or polypeptides, or agonists or antagonists of the present invention include, but are not limited to neoplasms located in the: colon, abdomen, bone, breast, digestive system, liver, pancreas, peritoneum, endocrine glands (adrenal, parathyroid,  
25 pituitary, testicles, ovary, thymus, thyroid), eye, head and neck, nervous (central and peripheral), lymphatic system, pelvic, skin, soft tissue, spleen, thoracic, and urogenital.

Similarly, other hyperproliferative disorders can also be treated or detected by polynucleotides or polypeptides, or agonists or antagonists of the present invention.  
30 Examples of such hyperproliferative disorders include, but are not limited to:

hypergammaglobulinemia, lymphoproliferative disorders, paraproteinemias, purpura, sarcoidosis, Sezary Syndrome, Waldenstrom's Macroglobulinemia, Gaucher's Disease, histiocytosis, and any other hyperproliferative disease, besides neoplasia, located in an organ system listed above.

- 5           One preferred embodiment utilizes polynucleotides of the present invention to inhibit aberrant cellular division, by gene therapy using the present invention, and/or protein fusions or fragments thereof.

          Thus, the present invention provides a method for treating cell proliferative disorders by inserting into an abnormally proliferating cell a polynucleotide of the  
10       present invention, wherein said polynucleotide represses said expression.

- Another embodiment of the present invention provides a method of treating cell-proliferative disorders in individuals comprising administration of one or more active gene copies of the present invention to an abnormally proliferating cell or cells. In a preferred embodiment, polynucleotides of the present invention is a DNA  
15       construct comprising a recombinant expression vector effective in expressing a DNA sequence encoding said polynucleotides. In another preferred embodiment of the present invention, the DNA construct encoding the polynucleotides of the present invention is inserted into cells to be treated utilizing a retrovirus, or more preferably an adenoviral vector (See G J. Nabel, et. al., PNAS 1999 96: 324-326, which is  
20       hereby incorporated by reference). In a most preferred embodiment, the viral vector is defective and will not transform non-proliferating cells, only proliferating cells. Moreover, in a preferred embodiment, the polynucleotides of the present invention inserted into proliferating cells either alone, or in combination with or fused to other polynucleotides, can then be modulated via an external stimulus (i.e. magnetic,  
25       specific small molecule, chemical, or drug administration, etc.), which acts upon the promoter upstream of said polynucleotides to induce expression of the encoded protein product. As such the beneficial therapeutic affect of the present invention may be expressly modulated (i.e. to increase, decrease, or inhibit expression of the present invention) based upon said external stimulus.



Polynucleotides of the present invention may be useful in repressing expression of oncogenic genes or antigens. By "repressing expression of the oncogenic genes " is intended the suppression of the transcription of the gene, the degradation of the gene transcript (pre-message RNA), the inhibition of splicing, the  
5 destruction of the messenger RNA, the prevention of the post-translational modifications of the protein, the destruction of the protein, or the inhibition of the normal function of the protein.

For local administration to abnormally proliferating cells, polynucleotides of the present invention may be administered by any method known to those of skill in  
10 the art including, but not limited to transfection, electroporation, microinjection of cells, or in vehicles such as liposomes, lipofectin, or as naked polynucleotides, or any other method described throughout the specification. The polynucleotide of the present invention may be delivered by known gene delivery systems such as, but not limited to, retroviral vectors (Gilboa, J. Virology 44:845 (1982); Hocke, Nature  
15 320:275 (1986); Wilson, et al., Proc. Natl. Acad. Sci. U.S.A. 85:3014), vaccinia virus system (Chakrabarty et al., Mol. Cell Biol. 5:3403 (1985) or other efficient DNA delivery systems (Yates et al., Nature 313:812 (1985)) known to those skilled in the art. These references are exemplary only and are hereby incorporated by reference. In order to specifically deliver or transfect cells which are abnormally proliferating  
20 and spare non-dividing cells, it is preferable to utilize a retrovirus, or adenoviral (as described in the art and elsewhere herein) delivery system known to those of skill in the art. Since host DNA replication is required for retroviral DNA to integrate and the retrovirus will be unable to self replicate due to the lack of the retrovirus genes needed for its life cycle. Utilizing such a retroviral delivery system for  
25 polynucleotides of the present invention will target said gene and constructs to abnormally proliferating cells and will spare the non-dividing normal cells.

The polynucleotides of the present invention may be delivered directly to cell proliferative disorder/disease sites in internal organs, body cavities and the like by use of imaging devices used to guide an injecting needle directly to the disease site. The

polynucleotides of the present invention may also be administered to disease sites at the time of surgical intervention.

By "cell proliferative disease" is meant any human or animal disease or disorder, affecting any one or any combination of organs, cavities, or body parts, which is characterized by single or multiple local abnormal proliferations of cells, groups of cells, or tissues, whether benign or malignant.

Any amount of the polynucleotides of the present invention may be administered as long as it has a biologically inhibiting effect on the proliferation of the treated cells. Moreover, it is possible to administer more than one of the polynucleotide of the present invention simultaneously to the same site. By "biologically inhibiting" is meant partial or total growth inhibition as well as decreases in the rate of proliferation or growth of the cells. The biologically inhibitory dose may be determined by assessing the effects of the polynucleotides of the present invention on target malignant or abnormally proliferating cell growth in tissue culture, tumor growth in animals and cell cultures, or any other method known to one of ordinary skill in the art.

The present invention is further directed to antibody-based therapies which involve administering of anti-polypeptides and anti-polynucleotide antibodies to a mammalian, preferably human, patient for treating one or more of the described disorders. Methods for producing anti-polypeptides and anti-polynucleotide antibodies polyclonal and monoclonal antibodies are described in detail elsewhere herein. Such antibodies may be provided in pharmaceutically acceptable compositions as known in the art or as described herein.

A summary of the ways in which the antibodies of the present invention may be used therapeutically includes binding polynucleotides or polypeptides of the present invention locally or systemically in the body or by direct cytotoxicity of the antibody, e.g. as mediated by complement (CDC) or by effector cells (ADCC). Some of these approaches are described in more detail below. Armed with the teachings provided herein, one of ordinary skill in the art will know how to use the antibodies of

the present invention for diagnostic, monitoring or therapeutic purposes without undue experimentation.

In particular, the antibodies, fragments and derivatives of the present invention are useful for treating a subject having or developing cell proliferative and/or differentiation disorders as described herein. Such treatment comprises administering  
5 a single or multiple doses of the antibody, or a fragment, derivative, or a conjugate thereof.

The antibodies of this invention may be advantageously utilized in combination with other monoclonal or chimeric antibodies, or with lymphokines or  
10 hematopoietic growth factors, for example., which serve to increase the number or activity of effector cells which interact with the antibodies.

It is preferred to use high affinity and/or potent in vivo inhibiting and/or neutralizing antibodies against polypeptides or polynucleotides of the present invention, fragments or regions thereof, for both immunoassays directed to and  
15 therapy of disorders related to polynucleotides or polypeptides, including fragments thereof, of the present invention. Such antibodies, fragments, or regions, will preferably have an affinity for polynucleotides or polypeptides, including fragments thereof. Preferred binding affinities include those with a dissociation constant or  $K_d$  less than  $5 \times 10^{-6}M$ ,  $10^{-6}M$ ,  $5 \times 10^{-7}M$ ,  $10^{-7}M$ ,  $5 \times 10^{-8}M$ ,  $10^{-8}M$ ,  $5 \times 10^{-9}M$ ,  $10^{-9}M$ ,  
20  $5 \times 10^{-10}M$ ,  $10^{-10}M$ ,  $5 \times 10^{-11}M$ ,  $10^{-11}M$ ,  $5 \times 10^{-12}M$ ,  $10^{-12}M$ ,  $5 \times 10^{-13}M$ ,  $10^{-13}M$ ,  $5 \times 10^{-14}M$ ,  $10^{-14}M$ ,  $5 \times 10^{-15}M$ , and  $10^{-15}M$ .

Moreover, polypeptides of the present invention are useful in inhibiting the angiogenesis of proliferative cells or tissues, either alone, as a protein fusion, or in combination with other polypeptides directly or indirectly, as described elsewhere  
25 herein. In a most preferred embodiment, said anti-angiogenesis effect may be achieved indirectly, for example, through the inhibition of hematopoietic, tumor-specific cells, such as tumor-associated macrophages (See Joseph IB, et al. J Natl Cancer Inst, 90(21):1648-53 (1998), which is hereby incorporated by reference). Antibodies directed to polypeptides or polynucleotides of the present invention may  
30 also result in inhibition of angiogenesis directly, or indirectly (See Witte L, et al.,

Cancer Metastasis Rev. 17(2):155-61 (1998), which is hereby incorporated by reference)).

Polypeptides, including protein fusions, of the present invention, or fragments thereof may be useful in inhibiting proliferative cells or tissues through the induction of apoptosis. Said polypeptides may act either directly, or indirectly to induce apoptosis of proliferative cells and tissues, for example in the activation of a death-domain receptor, such as tumor necrosis factor (TNF) receptor-1, CD95 (Fas/APO-1), TNF-receptor-related apoptosis-mediated protein (TRAMP) and TNF-related apoptosis-inducing ligand (TRAIL) receptor-1 and -2 (See Schulze-Osthoff K, et.al., Eur J Biochem 254(3):439-59 (1998), which is hereby incorporated by reference). Moreover, in another preferred embodiment of the present invention, said polypeptides may induce apoptosis through other mechanisms, such as in the activation of other proteins which will activate apoptosis, or through stimulating the expression of said proteins, either alone or in combination with small molecule drugs or adjuvants, such as apoptonin, galectins, thioredoxins, antiinflammatory proteins (See for example, Mutat Res 400(1-2):447-55 (1998), Med Hypotheses.50(5):423-33 (1998), Chem Biol Interact. Apr 24;111-112:23-34 (1998), J Mol Med.76(6):402-12 (1998), Int J Tissue React;20(1):3-15 (1998), which are all hereby incorporated by reference).

Polypeptides, including protein fusions to, or fragments thereof, of the present invention are useful in inhibiting the metastasis of proliferative cells or tissues. Inhibition may occur as a direct result of administering polypeptides, or antibodies directed to said polypeptides as described elsewhere herein, or indirectly, such as activating the expression of proteins known to inhibit metastasis, for example alpha 4 integrins, (See, e.g., Curr Top Microbiol Immunol 1998;231:125-41, which is hereby incorporated by reference). Such therapeutic affects of the present invention may be achieved either alone, or in combination with small molecule drugs or adjuvants.

In another embodiment, the invention provides a method of delivering compositions containing the polypeptides of the invention (e.g., compositions containing polypeptides or polypeptide antibodies associated with heterologous

polypeptides, heterologous nucleic acids, toxins, or prodrugs) to targeted cells expressing the polypeptide of the present invention. Polypeptides or polypeptide antibodies of the invention may be associated with heterologous polypeptides, heterologous nucleic acids, toxins, or prodrugs via hydrophobic, hydrophilic, ionic and/or covalent interactions. Polypeptides, protein fusions to, or fragments thereof, of the present invention are useful in enhancing the immunogenicity and/or antigenicity of proliferating cells or tissues, either directly, such as would occur if the polypeptides of the present invention 'vaccinated' the immune response to respond to proliferative antigens and immunogens, or indirectly, such as in activating the expression of proteins known to enhance the immune response (e.g. chemokines), to said antigens and immunogens.

#### **Cardiovascular Disorders**

Polynucleotides or polypeptides, or agonists or antagonists of the present invention, may be used to treat cardiovascular disorders, including peripheral artery disease, such as limb ischemia.

Cardiovascular disorders include cardiovascular abnormalities, such as arterio-arterial fistula, arteriovenous fistula, cerebral arteriovenous malformations, congenital heart defects, pulmonary atresia, and Scimitar Syndrome. Congenital heart defects include aortic coarctation, cor triatriatum, coronary vessel anomalies, crisscross heart, dextrocardia, patent ductus arteriosus, Ebstein's anomaly, Eisenmenger complex, hypoplastic left heart syndrome, levocardia, tetralogy of fallot, transposition of great vessels, double outlet right ventricle, tricuspid atresia, persistent truncus arteriosus, and heart septal defects, such as aortopulmonary septal defect, endocardial cushion defects, Lutembacher's Syndrome, trilog of Fallot, ventricular heart septal defects.

Cardiovascular disorders also include heart disease, such as arrhythmias, carcinoid heart disease, high cardiac output, low cardiac output, cardiac tamponade, endocarditis (including bacterial), heart aneurysm, cardiac arrest, congestive heart failure, congestive cardiomyopathy, paroxysmal dyspnea, cardiac edema, heart hypertrophy, congestive cardiomyopathy, left ventricular hypertrophy, right

ventricular hypertrophy, post-infarction heart rupture, ventricular septal rupture, heart valve diseases, myocardial diseases, myocardial ischemia, pericardial effusion, pericarditis (including constrictive and tuberculous), pneumopericardium, postpericardiotomy syndrome, pulmonary heart disease, rheumatic heart disease, ventricular dysfunction, hyperemia, cardiovascular pregnancy complications, Scimitar Syndrome, cardiovascular syphilis, and cardiovascular tuberculosis.

Arrhythmias include sinus arrhythmia, atrial fibrillation, atrial flutter, bradycardia, extrasystole, Adams-Stokes Syndrome, bundle-branch block, sinoatrial block, long QT syndrome, parasystole, Lown-Ganong-Levine Syndrome, Mahaim-type pre-excitation syndrome, Wolff-Parkinson-White syndrome, sick sinus syndrome, tachycardias, and ventricular fibrillation. Tachycardias include paroxysmal tachycardia, supraventricular tachycardia, accelerated idioventricular rhythm, atrioventricular nodal reentry tachycardia, ectopic atrial tachycardia, ectopic junctional tachycardia, sinoatrial nodal reentry tachycardia, sinus tachycardia, Torsades de Pointes, and ventricular tachycardia.

Heart valve disease include aortic valve insufficiency, aortic valve stenosis, hear murmurs, aortic valve prolapse, mitral valve prolapse, tricuspid valve prolapse, mitral valve insufficiency, mitral valve stenosis, pulmonary atresia, pulmonary valve insufficiency, pulmonary valve stenosis, tricuspid atresia, tricuspid valve insufficiency, and tricuspid valve stenosis.

Myocardial diseases include alcoholic cardiomyopathy, congestive cardiomyopathy, hypertrophic cardiomyopathy, aortic subvalvular stenosis, pulmonary subvalvular stenosis, restrictive cardiomyopathy, Chagas cardiomyopathy, endocardial fibroelastosis, endomyocardial fibrosis, Kearns Syndrome, myocardial reperfusion injury, and myocarditis.

Myocardial ischemias include coronary disease, such as angina pectoris, coronary aneurysm, coronary arteriosclerosis, coronary thrombosis, coronary vasospasm, myocardial infarction and myocardial stunning.

Cardiovascular diseases also include vascular diseases such as aneurysms, angiodyplasia, angiomatosis, bacillary angiomatosis, Hippel-Lindau Disease,

Klippel-Trenaunay-Weber Syndrome. Sturge-Weber Syndrome, angioneurotic edema, aortic diseases, Takayasu's Arteritis, aortitis, Leriche's Syndrome, arterial occlusive diseases, arteritis, enarteritis, polyarteritis nodosa, cerebrovascular disorders, diabetic angiopathies, diabetic retinopathy, embolisms, thrombosis, erythromelalgia, hemorrhoids, hepatic veno-occlusive disease, hypertension, hypotension, ischemia, peripheral vascular diseases, phlebitis, pulmonary veno-occlusive disease, Raynaud's disease, CREST syndrome, retinal vein occlusion, Scimitar syndrome, superior vena cava syndrome, telangiectasia, atacia telangiectasia, hereditary hemorrhagic telangiectasia, varicocele, varicose veins, varicose ulcer, vasculitis, and venous insufficiency.

Aneurysms include dissecting aneurysms, false aneurysms, infected aneurysms, ruptured aneurysms, aortic aneurysms, cerebral aneurysms, coronary aneurysms, heart aneurysms, and iliac aneurysms.

Arterial occlusive diseases include arteriosclerosis, intermittent claudication, carotid stenosis, fibromuscular dysplasias, mesenteric vascular occlusion, Moyamoya disease, renal artery obstruction, retinal artery occlusion, and thromboangiitis obliterans.

Cerebrovascular disorders include carotid artery diseases, cerebral amyloid angiopathy, cerebral aneurysm, cerebral anoxia, cerebral arteriosclerosis, cerebral arteriovenous malformation, cerebral artery diseases, cerebral embolism and thrombosis, carotid artery thrombosis, sinus thrombosis, Wallenberg's syndrome, cerebral hemorrhage, epidural hematoma, subdural hematoma, subarachnoid hemorrhage, cerebral infarction, cerebral ischemia (including transient), subclavian steal syndrome, periventricular leukomalacia, vascular headache, cluster headache, migraine, and vertebrobasilar insufficiency.

Embolisms include air embolisms, amniotic fluid embolisms, cholesterol embolisms, blue toe syndrome, fat embolisms, pulmonary embolisms, and thromboembolisms. Thrombosis include coronary thrombosis, hepatic vein thrombosis, retinal vein occlusion, carotid artery thrombosis, sinus thrombosis, Wallenberg's syndrome, and thrombophlebitis.

Ischemia includes cerebral ischemia, ischemic colitis, compartment syndromes, anterior compartment syndrome, myocardial ischemia, reperfusion injuries, and peripheral limb ischemia. Vasculitis includes aortitis, arteritis, Behcet's Syndrome, Churg-Strauss Syndrome, mucocutaneous lymph node syndrome, 5 thromboangiitis obliterans, hypersensitivity vasculitis, Schoenlein-Henoch purpura, allergic cutaneous vasculitis, and Wegener's granulomatosis.

Polynucleotides or polypeptides, or agonists or antagonists of the present invention, are especially effective for the treatment of critical limb ischemia and coronary disease.

10 Polypeptides may be administered using any method known in the art, including, but not limited to, direct needle injection at the delivery site, intravenous injection, topical administration, catheter infusion, biolistic injectors, particle accelerators, gelfoam sponge depots, other commercially available depot materials, osmotic pumps, oral or suppository solid pharmaceutical formulations, decanting or 15 topical applications during surgery, aerosol delivery. Such methods are known in the art. Polypeptides may be administered as part of a Therapeutic, described in more detail below. Methods of delivering polynucleotides are described in more detail herein.

#### 20 **Anti-Angiogenesis Activity**

The naturally occurring balance between endogenous stimulators and inhibitors of angiogenesis is one in which inhibitory influences predominate. Rastinejad *et al.*, *Cell* 56:345-355 (1989). In those rare instances in which neovascularization occurs under normal physiological conditions, such as wound 25 healing, organ regeneration, embryonic development, and female reproductive processes, angiogenesis is stringently regulated and spatially and temporally delimited. Under conditions of pathological angiogenesis such as that characterizing solid tumor growth, these regulatory controls fail. Unregulated angiogenesis becomes pathologic and sustains progression of many neoplastic and non-neoplastic diseases. 30 A number of serious diseases are dominated by abnormal neovascularization



including solid tumor growth and metastases, arthritis, some types of eye disorders, and psoriasis. See, e.g., reviews by Moses *et al.*, *Biotech.* 9:630-634 (1991); Folkman *et al.*, *N. Engl. J. Med.* 333:1757-1763 (1995); Auerbach *et al.*, *J. Microvasc. Res.* 29:401-411 (1985); Folkman, *Advances in Cancer Research*, eds. Klein and  
5 Weinhouse, Academic Press, New York, pp. 175-203 (1985); Patz, *Am. J. Ophthalmol.* 94:715-743 (1982); and Folkman *et al.*, *Science* 221:719-725 (1983). In a number of pathological conditions, the process of angiogenesis contributes to the disease state. For example, significant data have accumulated which suggest that the growth of solid tumors is dependent on angiogenesis. Folkman and Klagsbrun,  
10 *Science* 235:442-447 (1987).

The polynucleotides encoding a polypeptide of the present invention may be administered along with other polynucleotides encoding an angiogenic protein. Examples of angiogenic proteins include, but are not limited to, acidic and basic fibroblast growth factors, VEGF-1, VEGF-2, VEGF-3, epidermal growth factor alpha  
15 and beta, platelet-derived endothelial cell growth factor, platelet-derived growth factor, tumor necrosis factor alpha, hepatocyte growth factor, insulin like growth factor, colony stimulating factor, macrophage colony stimulating factor, granulocyte/macrophage colony stimulating factor, and nitric oxide synthase.

The present invention provides for treatment of diseases or disorders  
20 associated with neovascularization by administration of the polynucleotides and/or polypeptides of the invention, as well as agonists or antagonists of the present invention. Malignant and metastatic conditions which can be treated with the polynucleotides and polypeptides, or agonists or antagonists of the invention include, but are not limited to, malignancies, solid tumors, and cancers described herein and  
25 otherwise known in the art (for a review of such disorders, see Fishman *et al.*, *Medicine*, 2d Ed., J. B. Lippincott Co., Philadelphia (1985)). Thus, the present invention provides a method of treating an angiogenesis-related disease and/or disorder, comprising administering to an individual in need thereof a therapeutically effective amount of a polynucleotide, polypeptide, antagonist and/or agonist of the  
30 invention. For example, polynucleotides, polypeptides, antagonists and/or agonists

may be utilized in a variety of additional methods in order to therapeutically treat a cancer or tumor. Cancers which may be treated with polynucleotides, polypeptides, antagonists and/or agonists include, but are not limited to solid tumors, including prostate, lung, breast, ovarian, stomach, pancreas, larynx, esophagus, testes, liver, parotid, biliary tract, colon, rectum, cervix, uterus, endometrium, kidney, bladder, thyroid cancer; primary tumors and metastases; melanomas; glioblastoma; Kaposi's sarcoma; leiomyosarcoma; non-small cell lung cancer; colorectal cancer; advanced malignancies; and blood born tumors such as leukemias. For example, polynucleotides, polypeptides, antagonists and/or agonists may be delivered topically, in order to treat cancers such as skin cancer, head and neck tumors, breast tumors, and Kaposi's sarcoma.

Within yet other aspects, polynucleotides, polypeptides, antagonists and/or agonists may be utilized to treat superficial forms of bladder cancer by, for example, intravesical administration. Polynucleotides, polypeptides, antagonists and/or agonists may be delivered directly into the tumor, or near the tumor site, via injection or a catheter. Of course, as the artisan of ordinary skill will appreciate, the appropriate mode of administration will vary according to the cancer to be treated. Other modes of delivery are discussed herein.

Polynucleotides, polypeptides, antagonists and/or agonists may be useful in treating other disorders, besides cancers, which involve angiogenesis. These disorders include, but are not limited to: benign tumors, for example hemangiomas, acoustic neuromas, neurofibromas, trachomas, and pyogenic granulomas; arteriosclerotic plaques; ocular angiogenic diseases, for example, diabetic retinopathy, retinopathy of prematurity, macular degeneration, corneal graft rejection, neovascular glaucoma, retrolental fibroplasia, rubeosis, retinoblastoma, uveitis and Pterygia (abnormal blood vessel growth) of the eye; rheumatoid arthritis; psoriasis; delayed wound healing; endometriosis; vasculogenesis; granulations; hypertrophic scars (keloids); nonunion fractures; scleroderma; trachoma; vascular adhesions; myocardial angiogenesis; coronary collaterals; cerebral collaterals; arteriovenous malformations; ischemic limb angiogenesis; Osler-Webber Syndrome; plaque neovascularization;

telangiectasia; hemophilic joints; angiofibroma; fibromuscular dysplasia; wound granulation; Crohn's disease; and atherosclerosis.

For example, within one aspect of the present invention methods are provided for treating hypertrophic scars and keloids, comprising the step of administering a polynucleotide, polypeptide, antagonist and/or agonist of the invention to a hypertrophic scar or keloid.

Within one embodiment of the present invention polynucleotides, polypeptides, antagonists and/or agonists are directly injected into a hypertrophic scar or keloid, in order to prevent the progression of these lesions. This therapy is of particular value in the prophylactic treatment of conditions which are known to result in the development of hypertrophic scars and keloids (e.g., burns), and is preferably initiated after the proliferative phase has had time to progress (approximately 14 days after the initial injury), but before hypertrophic scar or keloid development. As noted above, the present invention also provides methods for treating neovascular diseases of the eye, including for example, corneal neovascularization, neovascular glaucoma, proliferative diabetic retinopathy, retrolental fibroplasia and macular degeneration.

Moreover, Ocular disorders associated with neovascularization which can be treated with the polynucleotides and polypeptides of the present invention (including agonists and/or antagonists) include, but are not limited to: neovascular glaucoma, diabetic retinopathy, retinoblastoma, retrolental fibroplasia, uveitis, retinopathy of prematurity macular degeneration, corneal graft neovascularization, as well as other eye inflammatory diseases, ocular tumors and diseases associated with choroidal or iris neovascularization. See, e.g., reviews by Waltman *et al.*, *Am. J. Ophthalm.* 85:704-710 (1978) and Gartner *et al.*, *Surv. Ophthalm.* 22:291-312 (1978).

Thus, within one aspect of the present invention methods are provided for treating neovascular diseases of the eye such as corneal neovascularization (including corneal graft neovascularization), comprising the step of administering to a patient a therapeutically effective amount of a compound (as described above) to the cornea, such that the formation of blood vessels is inhibited. Briefly, the cornea is a tissue which normally lacks blood vessels. In certain pathological conditions however,

capillaries may extend into the cornea from the pericorneal vascular plexus of the limbus. When the cornea becomes vascularized, it also becomes clouded, resulting in a decline in the patient's visual acuity. Visual loss may become complete if the cornea completely opacitates. A wide variety of disorders can result in corneal neovascularization, including for example, corneal infections (e.g., trachoma, herpes simplex keratitis, leishmaniasis and onchocerciasis), immunological processes (e.g., graft rejection and Stevens-Johnson's syndrome), alkali burns, trauma, inflammation (of any cause), toxic and nutritional deficiency states, and as a complication of wearing contact lenses.

10           Within particularly preferred embodiments of the invention, may be prepared for topical administration in saline (combined with any of the preservatives and antimicrobial agents commonly used in ocular preparations), and administered in eyedrop form. The solution or suspension may be prepared in its pure form and administered several times daily. Alternatively, anti-angiogenic compositions, 15 prepared as described above, may also be administered directly to the cornea. Within preferred embodiments, the anti-angiogenic composition is prepared with a muco-adhesive polymer which binds to cornea. Within further embodiments, the anti-angiogenic factors or anti-angiogenic compositions may be utilized as an adjunct to conventional steroid therapy. Topical therapy may also be useful prophylactically in 20 corneal lesions which are known to have a high probability of inducing an angiogenic response (such as chemical burns). In these instances the treatment, likely in combination with steroids, may be instituted immediately to help prevent subsequent complications.

          Within other embodiments, the compounds described above may be injected 25 directly into the corneal stroma by an ophthalmologist under microscopic guidance. The preferred site of injection may vary with the morphology of the individual lesion, but the goal of the administration would be to place the composition at the advancing front of the vasculature (i.e., interspersed between the blood vessels and the normal cornea). In most cases this would involve perilimbal corneal injection to "protect" the 30 cornea from the advancing blood vessels. This method may also be utilized shortly

after a corneal insult in order to prophylactically prevent corneal neovascularization. In this situation the material could be injected in the perilimbic cornea interspersed between the corneal lesion and its undesired potential limbic blood supply. Such methods may also be utilized in a similar fashion to prevent capillary invasion of transplanted corneas. In a sustained-release form injections might only be required 2-3 times per year. A steroid could also be added to the injection solution to reduce inflammation resulting from the injection itself.

Within another aspect of the present invention, methods are provided for treating neovascular glaucoma, comprising the step of administering to a patient a therapeutically effective amount of a polynucleotide, polypeptide, antagonist and/or agonist to the eye, such that the formation of blood vessels is inhibited. In one embodiment, the compound may be administered topically to the eye in order to treat early forms of neovascular glaucoma. Within other embodiments, the compound may be implanted by injection into the region of the anterior chamber angle. Within other embodiments, the compound may also be placed in any location such that the compound is continuously released into the aqueous humor. Within another aspect of the present invention, methods are provided for treating proliferative diabetic retinopathy, comprising the step of administering to a patient a therapeutically effective amount of a polynucleotide, polypeptide, antagonist and/or agonist to the eyes, such that the formation of blood vessels is inhibited.

Within particularly preferred embodiments of the invention, proliferative diabetic retinopathy may be treated by injection into the aqueous humor or the vitreous, in order to increase the local concentration of the polynucleotide, polypeptide, antagonist and/or agonist in the retina. Preferably, this treatment should be initiated prior to the acquisition of severe disease requiring photocoagulation.

Within another aspect of the present invention, methods are provided for treating retrolental fibroplasia, comprising the step of administering to a patient a therapeutically effective amount of a polynucleotide, polypeptide, antagonist and/or agonist to the eye, such that the formation of blood vessels is inhibited. The

compound may be administered topically, via intravitreal injection and/or via intraocular implants.

Additionally, disorders which can be treated with the polynucleotides, polypeptides, agonists and/or agonists include, but are not limited to, hemangioma, arthritis, psoriasis, angiofibroma, atherosclerotic plaques, delayed wound healing, granulations, hemophilic joints, hypertrophic scars, nonunion fractures, Osler-Weber syndrome, pyogenic granuloma, scleroderma, trachoma, and vascular adhesions.

Moreover, disorders and/or states, which can be treated with the the polynucleotides, polypeptides, agonists and/or agonists include, but are not limited to, solid tumors, blood born tumors such as leukemias, tumor metastasis, Kaposi's sarcoma, benign tumors, for example hemangiomas, acoustic neuromas, neurofibromas, trachomas, and pyogenic granulomas, rheumatoid arthritis, psoriasis, ocular angiogenic diseases, for example, diabetic retinopathy, retinopathy of prematurity, macular degeneration, corneal graft rejection, neovascular glaucoma, retrolental fibroplasia, rubeosis, retinoblastoma, and uveitis, delayed wound healing, endometriosis, vasculogenesis, granulations, hypertrophic scars (keloids), nonunion fractures, scleroderma, trachoma, vascular adhesions, myocardial angiogenesis, coronary collaterals, cerebral collaterals, arteriovenous malformations, ischemic limb angiogenesis, Osler-Webber Syndrome, plaque neovascularization, telangiectasia, hemophilic joints, angiofibroma fibromuscular dysplasia, wound granulation, Crohn's disease, atherosclerosis, birth control agent by preventing vascularization required for embryo implantation controlling menstruation, diseases that have angiogenesis as a pathologic consequence such as cat scratch disease (*Rochelominalia quintosa*), ulcers (*Helicobacter pylori*), Bartonellosis and bacillary angiomatosis.

In one aspect of the birth control method, an amount of the compound sufficient to block embryo implantation is administered before or after intercourse and fertilization have occurred, thus providing an effective method of birth control, possibly a "morning after" method. Polynucleotides, polypeptides, agonists and/or agonists may also be used in controlling menstruation or administered as either a

peritoneal lavage fluid or for peritoneal implantation in the treatment of endometriosis.

Polynucleotides, polypeptides, agonists and/or agonists of the present invention may be incorporated into surgical sutures in order to prevent stitch  
5 granulomas.

Polynucleotides, polypeptides, agonists and/or agonists may be utilized in a wide variety of surgical procedures. For example, within one aspect of the present invention a compositions (in the form of, for example, a spray or film) may be utilized to coat or spray an area prior to removal of a tumor, in order to isolate normal  
10 surrounding tissues from malignant tissue, and/or to prevent the spread of disease to surrounding tissues. Within other aspects of the present invention, compositions (e.g., in the form of a spray) may be delivered via endoscopic procedures in order to coat tumors, or inhibit angiogenesis in a desired locale. Within yet other aspects of the present invention, surgical meshes which have been coated with anti- angiogenic  
15 compositions of the present invention may be utilized in any procedure wherein a surgical mesh might be utilized. For example, within one embodiment of the invention a surgical mesh laden with an anti-angiogenic composition may be utilized during abdominal cancer resection surgery (e.g., subsequent to colon resection) in order to provide support to the structure, and to release an amount of the anti-  
20 angiogenic factor.

Within further aspects of the present invention, methods are provided for treating tumor excision sites, comprising administering a polynucleotide, polypeptide, agonist and/or agonist to the resection margins of a tumor subsequent to excision, such that the local recurrence of cancer and the formation of new blood vessels at the  
25 site is inhibited. Within one embodiment of the invention, the anti-angiogenic compound is administered directly to the tumor excision site (e.g., applied by swabbing, brushing or otherwise coating the resection margins of the tumor with the anti-angiogenic compound). Alternatively, the anti-angiogenic compounds may be incorporated into known surgical pastes prior to administration. Within particularly

preferred embodiments of the invention, the anti-angiogenic compounds are applied after hepatic resections for malignancy, and after neurosurgical operations.

Within one aspect of the present invention, polynucleotides, polypeptides, agonists and/or agonists may be administered to the resection margin of a wide variety of tumors, including for example, breast, colon, brain and hepatic tumors. For example, within one embodiment of the invention, anti-angiogenic compounds may be administered to the site of a neurological tumor subsequent to excision, such that the formation of new blood vessels at the site are inhibited.

The polynucleotides, polypeptides, agonists and/or agonists of the present invention may also be administered along with other anti-angiogenic factors. Representative examples of other anti-angiogenic factors include: Anti-Invasive Factor, retinoic acid and derivatives thereof, paclitaxel, Suramin, Tissue Inhibitor of Metalloproteinase-1, Tissue Inhibitor of Metalloproteinase-2, Plasminogen Activator Inhibitor-1, Plasminogen Activator Inhibitor-2, and various forms of the lighter "d group" transition metals.

Lighter "d group" transition metals include, for example, vanadium, molybdenum, tungsten, titanium, niobium, and tantalum species. Such transition metal species may form transition metal complexes. Suitable complexes of the above-mentioned transition metal species include oxo transition metal complexes.

Representative examples of vanadium complexes include oxo vanadium complexes such as vanadate and vanadyl complexes. Suitable vanadate complexes include metavanadate and orthovanadate complexes such as, for example, ammonium metavanadate, sodium metavanadate, and sodium orthovanadate. Suitable vanadyl complexes include, for example, vanadyl acetylacetonate and vanadyl sulfate including vanadyl sulfate hydrates such as vanadyl sulfate mono- and trihydrates.

Representative examples of tungsten and molybdenum complexes also include oxo complexes. Suitable oxo tungsten complexes include tungstate and tungsten oxide complexes. Suitable tungstate complexes include ammonium tungstate, calcium tungstate, sodium tungstate dihydrate, and tungstic acid. Suitable tungsten oxides include tungsten (IV) oxide and tungsten (VI) oxide. Suitable oxo



molybdenum complexes include molybdate, molybdenum oxide, and molybdenyl complexes. Suitable molybdate complexes include ammonium molybdate and its hydrates, sodium molybdate and its hydrates, and potassium molybdate and its hydrates. Suitable molybdenum oxides include molybdenum (VI) oxide, molybdenum (VI) oxide, and molybdic acid. Suitable molybdenyl complexes include, for example, molybdenyl acetylacetonate. Other suitable tungsten and molybdenum complexes include hydroxo derivatives derived from, for example, glycerol, tartaric acid, and sugars.

A wide variety of other anti-angiogenic factors may also be utilized within the context of the present invention. Representative examples include platelet factor 4; protamine sulphate; sulphated chitin derivatives (prepared from queen crab shells), (Murata et al., Cancer Res. 51:22-26, 1991); Sulphated Polysaccharide Peptidoglycan Complex (SP- PG) (the function of this compound may be enhanced by the presence of steroids such as estrogen, and tamoxifen citrate); Staurosporine; modulators of matrix metabolism, including for example, proline analogs, cishydroxyproline, d,L-3,4-dehydroproline, Thiaproline, alpha,alpha-dipyridyl, aminopropionitrile fumarate; 4-propyl-5-(4-pyridinyl)-2(3H)-oxazolone; Methotrexate; Mitoxantrone; Heparin; Interferons; 2 Macroglobulin-serum; ChIMP-3 (Pavloff et al., J. Bio. Chem. 267:17321-17326, 1992); Chymostatin (Tomkinson et al., Biochem J. 286:475-480, 1992); Cyclodextrin Tetradasulfate; Eponemycin; Camptothecin; Fumagillin (Ingber et al., Nature 348:555-557, 1990); Gold Sodium Thiomalate ("GST"; Matsubara and Ziff, J. Clin. Invest. 79:1440-1446, 1987); anticollagenase-serum; alpha2-antiplasmin (Holmes et al., J. Biol. Chem. 262(4):1659-1664, 1987); Bisantrene (National Cancer Institute); Lobenzarit disodium (N-(2)-carboxyphenyl-4-chloroanthronilic acid disodium or "CCA"; Takeuchi et al., Agents Actions 36:312-316, 1992); Thalidomide; Angostatic steroid; AGM-1470; carboxynaminolimidazole; and metalloproteinase inhibitors such as BB94.

**Diseases at the Cellular Level**

Diseases associated with increased cell survival or the inhibition of apoptosis that could be treated or detected by polynucleotides or polypeptides, as well as antagonists or agonists of the present invention, include cancers (such as follicular lymphomas, carcinomas with p53 mutations, and hormone-dependent tumors, including, but not limited to colon cancer, cardiac tumors, pancreatic cancer, melanoma, retinoblastoma, glioblastoma, lung cancer, intestinal cancer, testicular cancer, stomach cancer, neuroblastoma, myxoma, myoma, lymphoma, endothelioma, osteoblastoma, osteoclastoma, osteosarcoma, chondrosarcoma, adenoma, breast cancer, prostate cancer, Kaposi's sarcoma and ovarian cancer); autoimmune disorders (such as, multiple sclerosis, Sjogren's syndrome, Hashimoto's thyroiditis, biliary cirrhosis, Behcet's disease, Crohn's disease, polymyositis, systemic lupus erythematosus and immune-related glomerulonephritis and rheumatoid arthritis) and viral infections (such as herpes viruses, pox viruses and adenoviruses), inflammation, graft v. host disease, acute graft rejection, and chronic graft rejection. In preferred embodiments, polynucleotides, polypeptides, and/or antagonists of the invention are used to inhibit growth, progression, and/or metasis of cancers, in particular those listed above.

Additional diseases or conditions associated with increased cell survival that could be treated or detected by polynucleotides or polypeptides, or agonists or antagonists of the present invention include, but are not limited to, progression, and/or metastases of malignancies and related disorders such as leukemia (including acute leukemias (e.g., acute lymphocytic leukemia, acute myelocytic leukemia (including myeloblastic, promyelocytic, myelomonocytic, monocytic, and erythroleukemia)) and chronic leukemias (e.g., chronic myelocytic (granulocytic) leukemia and chronic lymphocytic leukemia)), polycythemia vera, lymphomas (e.g., Hodgkin's disease and non-Hodgkin's disease), multiple myeloma, Waldenstrom's macroglobulinemia, heavy chain disease, and solid tumors including, but not limited to, sarcomas and carcinomas such as fibrosarcoma, myxosarcoma, liposarcoma, chondrosarcoma, osteogenic sarcoma, chordoma, angiosarcoma, endotheliosarcoma,

lymphangiosarcoma, lymphangioendotheliosarcoma, synovioma, mesothelioma, Ewing's tumor, leiomyosarcoma, rhabdomyosarcoma, colon carcinoma, pancreatic cancer, breast cancer, ovarian cancer, prostate cancer, squamous cell carcinoma, basal cell carcinoma, adenocarcinoma, sweat gland carcinoma, sebaceous gland carcinoma, papillary carcinoma, papillary adenocarcinomas, cystadenocarcinoma, medullary carcinoma, bronchogenic carcinoma, renal cell carcinoma, hepatoma, bile duct carcinoma, choriocarcinoma, seminoma, embryonal carcinoma, Wilm's tumor, cervical cancer, testicular tumor, lung carcinoma, small cell lung carcinoma, bladder carcinoma, epithelial carcinoma, glioma, astrocytoma, medulloblastoma, craniopharyngioma, ependymoma, pinealoma, hemangioblastoma, acoustic neuroma, oligodendroglioma, menangioma, melanoma, neuroblastoma, and retinoblastoma.

Diseases associated with increased apoptosis that could be treated or detected by polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, include AIDS; neurodegenerative disorders (such as Alzheimer's disease, Parkinson's disease, Amyotrophic lateral sclerosis, Retinitis pigmentosa, Cerebellar degeneration and brain tumor or prior associated disease); autoimmune disorders (such as, multiple sclerosis, Sjogren's syndrome, Hashimoto's thyroiditis, biliary cirrhosis, Behcet's disease, Crohn's disease, polymyositis, systemic lupus erythematosus and immune-related glomerulonephritis and rheumatoid arthritis) myelodysplastic syndromes (such as aplastic anemia), graft v. host disease, ischemic injury (such as that caused by myocardial infarction, stroke and reperfusion injury), liver injury (e.g., hepatitis related liver injury, ischemia/reperfusion injury, cholestosis (bile duct injury) and liver cancer); toxin-induced liver disease (such as that caused by alcohol), septic shock, cachexia and anorexia.

25

#### **Wound Healing and Epithelial Cell Proliferation**

In accordance with yet a further aspect of the present invention, there is provided a process for utilizing polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, for therapeutic purposes, for example, to stimulate epithelial cell proliferation and basal keratinocytes for the purpose of wound

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healing, and to stimulate hair follicle production and healing of dermal wounds. Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, may be clinically useful in stimulating wound healing including surgical wounds, excisional wounds, deep wounds involving damage of the dermis and epidermis, eye tissue wounds, dental tissue wounds, oral cavity wounds, diabetic  
5 ulcers, dermal ulcers, cubitus ulcers, arterial ulcers, venous stasis ulcers, burns resulting from heat exposure or chemicals, and other abnormal wound healing conditions such as uremia, malnutrition, vitamin deficiencies and complications associated with systemic treatment with steroids, radiation therapy and antineoplastic  
10 drugs and antimetabolites. Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, could be used to promote dermal reestablishment subsequent to dermal loss

Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, could be used to increase the adherence of skin grafts to a wound  
15 bed and to stimulate re-epithelialization from the wound bed. The following are types of grafts that polynucleotides or polypeptides, agonists or antagonists of the present invention, could be used to increase adherence to a wound bed: autografts, artificial skin, allografts, autodermic graft, autoepidermic grafts, avascular grafts, Blair-Brown grafts, bone graft, brephoplastic grafts, cutis graft, delayed graft, dermic graft, epidermic graft, fascia graft, full thickness graft, heterologous graft, xenograft,  
20 homologous graft, hyperplastic graft, lamellar graft, mesh graft, mucosal graft, Ollier-Thiersch graft, omentum graft, patch graft, pedicle graft, penetrating graft, split skin graft, thick split graft. Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, can be used to promote skin strength and to  
25 improve the appearance of aged skin.

It is believed that polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, will also produce changes in hepatocyte proliferation, and epithelial cell proliferation in the lung, breast, pancreas, stomach, small intestine, and large intestine. Polynucleotides or polypeptides, as well as  
30 agonists or antagonists of the present invention, could promote proliferation of

epithelial cells such as sebocytes, hair follicles, hepatocytes, type II pneumocytes, mucin-producing goblet cells, and other epithelial cells and their progenitors contained within the skin, lung, liver, and gastrointestinal tract. Polynucleotides or polypeptides, agonists or antagonists of the present invention, may promote  
5 proliferation of endothelial cells, keratinocytes, and basal keratinocytes.

Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, could also be used to reduce the side effects of gut toxicity that result from radiation, chemotherapy treatments or viral infections. Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, may have a  
10 cytoprotective effect on the small intestine mucosa. Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, may also stimulate healing of mucositis (mouth ulcers) that result from chemotherapy and viral infections.

Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, could further be used in full regeneration of skin in full and partial  
15 thickness skin defects, including burns, (i.e., repopulation of hair follicles, sweat glands, and sebaceous glands), treatment of other skin defects such as psoriasis. Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, could be used to treat epidermolysis bullosa, a defect in adherence of the epidermis to the underlying dermis which results in frequent, open and painful blisters  
20 by accelerating reepithelialization of these lesions. Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, could also be used to treat gastric and duodenal ulcers and help heal by scar formation of the mucosal lining and regeneration of glandular mucosa and duodenal mucosal lining more rapidly. Inflammatory bowel diseases, such as Crohn's disease and ulcerative colitis, are  
25 diseases which result in destruction of the mucosal surface of the small or large intestine, respectively. Thus, polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, could be used to promote the resurfacing of the mucosal surface to aid more rapid healing and to prevent progression of inflammatory bowel disease. Treatment with polynucleotides or polypeptides, agonists or  
30 antagonists of the present invention, is expected to have a significant effect on the

production of mucus throughout the gastrointestinal tract and could be used to protect the intestinal mucosa from injurious substances that are ingested or following surgery. Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, could be used to treat diseases associate with the under expression.

5           Moreover, polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, could be used to prevent and heal damage to the lungs due to various pathological states. Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, which could stimulate proliferation and differentiation and promote the repair of alveoli and brochiolar epithelium to prevent  
10 or treat acute or chronic lung damage. For example, emphysema, which results in the progressive loss of aveoli, and inhalation injuries, i.e., resulting from smoke inhalation and burns, that cause necrosis of the bronchiolar epithelium and alveoli could be effectively treated using polynucleotides or polypeptides, agonists or antagonists of the present invention. Also, polynucleotides or polypeptides, as well as  
15 agonists or antagonists of the present invention, could be used to stimulate the proliferation of and differentiation of type II pneumocytes, which may help treat or prevent disease such as hyaline membrane diseases, such as infant respiratory distress syndrome and bronchopulmonary displasia, in premature infants.

          Polynucleotides or polypeptides, as well as agonists or antagonists of the  
20 present invention, could stimulate the proliferation and differentiation of hepatocytes and, thus, could be used to alleviate or treat liver diseases and pathologies such as fulminant liver failure caused by cirrhosis, liver damage caused by viral hepatitis and toxic substances (i.e., acetaminophen, carbon tetraholoride and other hepatotoxins known in the art).

25           In addition, polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, could be used treat or prevent the onset of diabetes mellitus. In patients with newly diagnosed Types I and II diabetes, where some islet cell function remains, polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, could be used to maintain the islet function so as to alleviate,  
30 delay or prevent permanent manifestation of the disease. Also, polynucleotides or

polypeptides, as well as agonists or antagonists of the present invention, could be used as an auxiliary in islet cell transplantation to improve or promote islet cell function.

## 5 **Neurological Diseases**

In accordance with yet a further aspect of the present invention, there is provided a process for utilizing polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, for therapeutic purposes, for example, to  
10 stimulate neurological cell proliferation and/or differentiation. Therefore, polynucleotides, polypeptides, agonists and/or antagonists of the invention may be used to treat and/or detect neurologic diseases. Moreover, polynucleotides or polypeptides, or agonists or antagonists of the invention, can be used as a marker or detector of a particular nervous system disease or disorder.

15 Examples of neurologic diseases which can be treated or detected with polynucleotides, polypeptides, agonists, and/or antagonists of the present invention include brain diseases, such as metabolic brain diseases which includes phenylketonuria such as maternal phenylketonuria, pyruvate carboxylase deficiency, pyruvate dehydrogenase complex deficiency, Wernicke's Encephalopathy, brain  
20 edema, brain neoplasms such as cerebellar neoplasms which include infratentorial neoplasms, cerebral ventricle neoplasms such as choroid plexus neoplasms, hypothalamic neoplasms, supratentorial neoplasms, canavan disease, cerebellar diseases such as cerebellar ataxia which include spinocerebellar degeneration such as ataxia telangiectasia, cerebellar dyssynergia, Friederich's Ataxia, Machado-Joseph  
25 Disease, olivopontocerebellar atrophy, cerebellar neoplasms such as infratentorial neoplasms, diffuse cerebral sclerosis such as encephalitis periaxialis, globoid cell leukodystrophy, metachromatic leukodystrophy and subacute sclerosing panencephalitis, cerebrovascular disorders (such as carotid artery diseases which include carotid artery thrombosis, carotid stenosis and Moyamoya Disease, cerebral  
30 amyloid angiopathy, cerebral aneurysm, cerebral anoxia, cerebral arteriosclerosis, cerebral arteriovenous malformations, cerebral artery diseases, cerebral embolism and

thrombosis such as carotid artery thrombosis, sinus thrombosis and Wallenberg's Syndrome, cerebral hemorrhage such as epidural hematoma, subdural hematoma and subarachnoid hemorrhage, cerebral infarction, cerebral ischemia such as transient cerebral ischemia, Subclavian Steal Syndrome and vertebrobasilar insufficiency, 5 vascular dementia such as multi-infarct dementia, periventricular leukomalacia, vascular headache such as cluster headache, migraine, dementia such as AIDS Dementia Complex, presenile dementia such as Alzheimer's Disease and Creutzfeldt-Jakob Syndrome, senile dementia such as Alzheimer's Disease and progressive supranuclear palsy, vascular dementia such as multi-infarct dementia, encephalitis 10 which include encephalitis periaxialis, viral encephalitis such as epidemic encephalitis, Japanese Encephalitis, St. Louis Encephalitis, tick-borne encephalitis and West Nile Fever, acute disseminated encephalomyelitis, meningoencephalitis such as uveomeningoencephalitic syndrome, Postencephalitic Parkinson Disease and subacute sclerosing panencephalitis, encephalomalacia such as periventricular 15 leukomalacia, epilepsy such as generalized epilepsy which includes infantile spasms, absence epilepsy, myoclonic epilepsy which includes MERRF Syndrome, tonic-clonic epilepsy, partial epilepsy such as complex partial epilepsy, frontal lobe epilepsy and temporal lobe epilepsy, post-traumatic epilepsy, status epilepticus such as Epilepsia Partialis Continua, Hallervorden-Spatz Syndrome, hydrocephalus such as 20 Dandy-Walker Syndrome and normal pressure hydrocephalus, hypothalamic diseases such as hypothalamic neoplasms, cerebral malaria, narcolepsy which includes cataplexy, bulbar poliomyelitis, cerebri pseudotumor, Rett Syndrome, Reye's Syndrome, thalamic diseases, cerebral toxoplasmosis, intracranial tuberculoma and Zellweger Syndrome, central nervous system infections such as AIDS Dementia 25 Complex, Brain Abscess, subdural empyema, encephalomyelitis such as Equine Encephalomyelitis, Venezuelan Equine Encephalomyelitis, Necrotizing Hemorrhagic Encephalomyelitis, Visna, cerebral malaria, meningitis such as arachnoiditis, aseptic meningitis such as viral meningitis which includes lymphocytic choriomeningitis. Bacterial meningitis which includes Haemophilus Meningitis, Listeria Meningitis, 30 Meningococcal Meningitis such as Waterhouse-Friderichsen Syndrome,



Pneumococcal Meningitis and meningeal tuberculosis, fungal meningitis such as Cryptococcal Meningitis, subdural effusion, meningoencephalitis such as uvemeningoencephalitic syndrome, myelitis such as transverse myelitis, neurosyphilis such as tabes dorsalis, poliomyelitis which includes bulbar poliomyelitis and postpoliomyelitis syndrome, prion diseases (such as Creutzfeldt-Jakob Syndrome, Bovine Spongiform Encephalopathy, Gerstmann-Straussler Syndrome, Kuru, Scrapie) cerebral toxoplasmosis, central nervous system neoplasms such as brain neoplasms that include cerebellar neoplasms such as infratentorial neoplasms, cerebral ventricle neoplasms such as choroid plexus neoplasms, hypothalamic neoplasms and supratentorial neoplasms, meningeal neoplasms, spinal cord neoplasms which include epidural neoplasms, demyelinating diseases such as Canavan Diseases, diffuse cerebral sclerolitis which includes adrenoleukodystrophy, encephalitis periaxialis, globoid cell leukodystrophy, diffuse cerebral sclerosis such as metachromatic leukodystrophy, allergic encephalomyelitis, necrotizing hemorrhagic encephalomyelitis, progressive multifocal leukoencephalopathy, multiple sclerosis, central pontine myelinolysis, transverse myelitis, neuromyelitis optica, Scrapie, Swayback, Chronic Fatigue Syndrome, Visna, High Pressure Nervous Syndrome, Meningism, spinal cord diseases such as amyotonia congenita, amyotrophic lateral sclerosis, spinal muscular atrophy such as Werdnig-Hoffmann Disease, spinal cord compression, spinal cord neoplasms such as epidural neoplasms, syringomyelia, Tabes Dorsalis, Stiff-Man Syndrome, mental retardation such as Angelman Syndrome, Cri-du-Chat Syndrome, De Lange's Syndrome, Down Syndrome, Gangliosidoses such as gangliosidoses G(M1), Sandhoff Disease, Tay-Sachs Disease, Hartnup Disease, homocystinuria, Laurence-Moon- Biedl Syndrome, Lesch-Nyhan Syndrome, Maple Syrup Urine Disease, mucopolysaccharidosis such as fucosidosis, neuronal ceroid-lipofuscinosis, oculocerebrorenal syndrome, phenylketonuria such as maternal phenylketonuria, Prader-Willi Syndrome, Rett Syndrome, Rubinstein-Taybi Syndrome, Tuberous Sclerosis, WAGR Syndrome, nervous system abnormalities such as holoprosencephaly, neural tube defects such as anencephaly which includes hydranencephaly, Arnold-Chiari Deformity, encephalocele, meningocele,

meningomyelocele, spinal dysraphism such as spina bifida cystica and spina bifida occulta, hereditary motor and sensory neuropathies which include Charcot-Marie Disease, Hereditary optic atrophy, Refsum's Disease, hereditary spastic paraplegia, Werdnig-Hoffmann Disease, Hereditary Sensory and Autonomic Neuropathies such

5 as Congenital Analgesia and Familial Dysautonomia, Neurologic manifestations (such as agnosia that include Gerstmann's Syndrome, Amnesia such as retrograde amnesia, apraxia, neurogenic bladder, cataplexy, communicative disorders such as hearing disorders that includes deafness, partial hearing loss, loudness recruitment and tinnitus, language disorders such as aphasia which include agraphia, anomia,

10 broca aphasia, and Wernicke Aphasia, Dyslexia such as Acquired Dyslexia, language development disorders, speech disorders such as aphasia which includes anomia, broca aphasia and Wernicke Aphasia, articulation disorders, communicative disorders such as speech disorders which include dysarthria, echolalia, mutism and stuttering, voice disorders such as aphonia and hoarseness, decerebrate state, delirium,

15 fasciculation, hallucinations, meningism, movement disorders such as angelman syndrome, ataxia, athetosis, chorea, dystonia, hypokinesia, muscle hypotonia, myoclonus, tic, torticollis and tremor, muscle hypertonia such as muscle rigidity such as stiff-man syndrome, muscle spasticity, paralysis such as facial paralysis which includes Herpes Zoster Oticus, Gastroparesis, Hemiplegia, ophthalmoplegia such as

20 diplopia, Duane's Syndrome, Horner's Syndrome, Chronic progressive external ophthalmoplegia such as Kearns Syndrome, Bulbar Paralysis, Tropical Spastic Paraparesis, Paraplegia such as Brown-Sequard Syndrome, quadriplegia, respiratory paralysis and vocal cord paralysis, paresis, phantom limb, taste disorders such as ageusia and dysgeusia, vision disorders such as amblyopia, blindness, color vision

25 defects, diplopia, hemianopsia, scotoma and subnormal vision, sleep disorders such as hypersomnia which includes Kleine-Levin Syndrome, insomnia, and somnambulism, spasm such as trismus, unconsciousness such as coma, persistent vegetative state and syncope and vertigo, neuromuscular diseases such as amyotonia congenita, amyotrophic lateral sclerosis, Lambert-Eaton Myasthenic Syndrome, motor neuron

30 disease, muscular atrophy such as spinal muscular atrophy, Charcot-Marie Disease

and Werdnig-Hoffmann Disease, Postpoliomyelitis Syndrome, Muscular Dystrophy, Myasthenia Gravis, Myotonia Atrophica, Myotonia Confenita, Nemaline Myopathy, Familial Periodic Paralysis, Multiplex Paramyoclonus, Tropical Spastic Paraparesis and Stiff-Man Syndrome, peripheral nervous system diseases such as acrodynia, amyloid neuropathies, autonomic nervous system diseases such as Adie's Syndrome, Barre-Lieou Syndrome, Familial Dysautonomia, Horner's Syndrome, Reflex Sympathetic Dystrophy and Shy-Drager Syndrome, Cranial Nerve Diseases such as Acoustic Nerve Diseases such as Acoustic Neuroma which includes Neurofibromatosis 2, Facial Nerve Diseases such as Facial Neuralgia, Melkersson-Rosenthal Syndrome, ocular motility disorders which includes amblyopia, nystagmus, oculomotor nerve paralysis, ophthalmoplegia such as Duane's Syndrome, Horner's Syndrome, Chronic Progressive External Ophthalmoplegia which includes Kearns Syndrome, Strabismus such as Esotropia and Exotropia, Oculomotor Nerve Paralysis, Optic Nerve Diseases such as Optic Atrophy which includes Hereditary Optic Atrophy, Optic Disk Drusen, Optic Neuritis such as Neuromyelitis Optica, Papilledema, Trigeminal Neuralgia, Vocal Cord Paralysis, Demyelinating Diseases such as Neuromyelitis Optica and Swayback, Diabetic neuropathies such as diabetic foot, nerve compression syndromes such as carpal tunnel syndrome, tarsal tunnel syndrome, thoracic outlet syndrome such as cervical rib syndrome, ulnar nerve compression syndrome, neuralgia such as causalgia, cervico-brachial neuralgia, facial neuralgia and trigeminal neuralgia, neuritis such as experimental allergic neuritis, optic neuritis, polyneuritis, polyradiculoneuritis and radiculitis such as polyradiculitis, hereditary motor and sensory neuropathies such as Charcot-Marie Disease, Hereditary Optic Atrophy, Refsum's Disease, Hereditary Spastic Paraplegia and Werdnig-Hoffmann Disease, Hereditary Sensory and Autonomic Neuropathies which include Congenital Analgesia and Familial Dysautonomia, POEMS Syndrome, Sciatica, Gustatory Sweating and Tetany).

### **Infectious Disease**

Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention can be used to treat or detect infectious agents. For example, by increasing the immune response, particularly increasing the proliferation and differentiation of B and/or T cells, infectious diseases may be treated. The immune response may be increased by either enhancing an existing immune response, or by initiating a new immune response. Alternatively, polynucleotides or polypeptides, as well as agonists or antagonists of the present invention may also directly inhibit the infectious agent, without necessarily eliciting an immune response.

Viruses are one example of an infectious agent that can cause disease or symptoms that can be treated or detected by a polynucleotide or polypeptide and/or agonist or antagonist of the present invention. Examples of viruses, include, but are not limited to Examples of viruses, include, but are not limited to the following DNA and RNA viruses and viral families: Arbovirus, Adenoviridae, Arenaviridae, Arterivirus, Birnaviridae, Bunyaviridae, Caliciviridae, Circoviridae, Coronaviridae, Dengue, EBV, HIV, Flaviviridae, Hepadnaviridae (Hepatitis), Herpesviridae (such as, Cytomegalovirus, Herpes Simplex, Herpes Zoster), Mononegavirus (e.g., Paramyxoviridae, Morbillivirus, Rhabdoviridae), Orthomyxoviridae (e.g., Influenza A, Influenza B, and parainfluenza), Papiloma virus, Papovaviridae, Parvoviridae, Picornaviridae, Poxviridae (such as Smallpox or Vaccinia), Reoviridae (e.g., Rotavirus), Retroviridae (HTLV-I, HTLV-II, Lentivirus), and Togaviridae (e.g., Rubivirus). Viruses falling within these families can cause a variety of diseases or symptoms, including, but not limited to: arthritis, bronchiollitis, respiratory syncytial virus, encephalitis, eye infections (e.g., conjunctivitis, keratitis), chronic fatigue syndrome, hepatitis (A, B, C, E, Chronic Active, Delta), Japanese B encephalitis, Junin, Chikungunya, Rift Valley fever, yellow fever, meningitis, opportunistic infections (e.g., AIDS), pneumonia, Burkitt's Lymphoma, chickenpox, hemorrhagic fever, Measles, Mumps, Parainfluenza, Rabies, the common cold, Polio, leukemia, Rubella, sexually transmitted diseases, skin diseases (e.g., Kaposi's, warts), and viremia. polynucleotides or polypeptides, or agonists or antagonists of the invention, can be used to treat or detect any of these symptoms or diseases. In specific

embodiments, polynucleotides, polypeptides, or agonists or antagonists of the invention are used to treat: meningitis, Dengue, EBV, and/or hepatitis (e.g., hepatitis B). In an additional specific embodiment polynucleotides, polypeptides, or agonists or antagonists of the invention are used to treat patients nonresponsive to one or more  
5 other commercially available hepatitis vaccines. In a further specific embodiment polynucleotides, polypeptides, or agonists or antagonists of the invention are used to treat AIDS.

Similarly, bacterial or fungal agents that can cause disease or symptoms and that can be treated or detected by a polynucleotide or polypeptide and/or agonist or  
10 antagonist of the present invention include, but not limited to, include, but not limited to, the following Gram-Negative and Gram-positive bacteria and bacterial families and fungi: Actinomycetales (e.g., Corynebacterium, Mycobacterium, Nocardia), Cryptococcus neoformans, Aspergillosis, Bacillaceae (e.g., Anthrax, Clostridium), Bacteroidaceae, Blastomycosis, Bordetella, Borrelia (e.g., Borrelia burgdorferi,  
15 Brucellosis, Candidiasis, Campylobacter, Coccidioidomycosis, Cryptococcosis, Dermatocycoses, E. coli (e.g., Enterotoxigenic E. coli and Enterohemorrhagic E. coli), Enterobacteriaceae (Klebsiella, Salmonella (e.g., Salmonella typhi, and Salmonella paratyphi), Serratia, Yersinia), Erysipelothrix, Helicobacter, Legionellosis, Leptospirosis, Listeria, Mycoplasmatales, Mycobacterium leprae,  
20 Vibrio cholerae, Neisseriaceae (e.g., Acinetobacter, Gonorrhea, Meningococcal), Meisseria meningitidis, Pasteurellacea Infections (e.g., Actinobacillus, Heamophilus (e.g., Heamophilus influenza type B), Pasteurella), Pseudomonas, Rickettsiaceae, Chlamydiaceae, Syphilis, Shigella spp., Staphylococcal, Meningiococcal, Pneumococcal and Streptococcal (e.g., Streptococcus pneumoniae and Group B  
25 Streptococcus). These bacterial or fungal families can cause the following diseases or symptoms, including, but not limited to: bacteremia, endocarditis, eye infections (conjunctivitis, tuberculosis, uveitis), gingivitis, opportunistic infections (e.g., AIDS related infections), paronychia, prosthesis-related infections, Reiter's Disease, respiratory tract infections, such as Whooping Cough or Empyema, sepsis, Lyme  
30 Disease, Cat-Scratch Disease, Dysentery, Paratyphoid Fever, food poisoning,

Typhoid, pneumonia, Gonorrhea, meningitis (e.g., meningitis types A and B), Chlamydia, Syphilis, Diphtheria, Leprosy, Paratuberculosis, Tuberculosis, Lupus, Botulism, gangrene, tetanus, impetigo, Rheumatic Fever, Scarlet Fever, sexually transmitted diseases, skin diseases (e.g., cellulitis, dermatocycoses), toxemia, urinary tract infections, wound infections. Polynucleotides or polypeptides, agonists or antagonists of the invention, can be used to treat or detect any of these symptoms or diseases. In specific embodiments, Polynucleotides, polypeptides, agonists or antagonists of the invention are used to treat: tetanus, Diphtheria, botulism, and/or meningitis type B.

Moreover, parasitic agents causing disease or symptoms that can be treated or detected by a polynucleotide or polypeptide and/or agonist or antagonist of the present invention include, but not limited to, the following families or class: Amebiasis, Babesiosis, Coccidiosis, Cryptosporidiosis, Dientamoebiasis, Dourine, Ectoparasitic, Giardiasis, Helminthiasis, Leishmaniasis, Theileriasis, Toxoplasmosis, Trypanosomiasis, and Trichomonas and Sporozoans (e.g., Plasmodium virax, Plasmodium falciparum, Plasmodium malariae and Plasmodium ovale). These parasites can cause a variety of diseases or symptoms, including, but not limited to: Scabies, Trombiculiasis, eye infections, intestinal disease (e.g., dysentery, giardiasis), liver disease, lung disease, opportunistic infections (e.g., AIDS related), malaria, pregnancy complications, and toxoplasmosis. polynucleotides or polypeptides, or agonists or antagonists of the invention, can be used to treat or detect any of these symptoms or diseases.

Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention of the present invention could either be by administering an effective amount of a polypeptide to the patient, or by removing cells from the patient, supplying the cells with a polynucleotide of the present invention, and returning the engineered cells to the patient (ex vivo therapy). Moreover, the polypeptide or polynucleotide of the present invention can be used as an antigen in a vaccine to raise an immune response against infectious disease.

### Regeneration

Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention can be used to differentiate, proliferate, and attract cells, leading to the regeneration of tissues. (See, Science 276:59-87 (1997).) The regeneration of  
5 tissues could be used to repair, replace, or protect tissue damaged by congenital defects, trauma (wounds, burns, incisions, or ulcers), age, disease (e.g. osteoporosis, osteoarthritis, periodontal disease, liver failure), surgery, including cosmetic plastic surgery, fibrosis, reperfusion injury, or systemic cytokine damage.

Tissues that could be regenerated using the present invention include organs  
10 (e.g., pancreas, liver, intestine, kidney, skin, endothelium), muscle (smooth, skeletal or cardiac), vasculature (including vascular and lymphatics), nervous, hematopoietic, and skeletal (bone, cartilage, tendon, and ligament) tissue. Preferably, regeneration occurs without or decreased scarring. Regeneration also may include angiogenesis.

Moreover, polynucleotides or polypeptides, as well as agonists or antagonists  
15 of the present invention, may increase regeneration of tissues difficult to heal. For example, increased tendon/ligament regeneration would quicken recovery time after damage. Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention could also be used prophylactically in an effort to avoid damage. Specific diseases that could be treated include of tendinitis, carpal tunnel syndrome,  
20 and other tendon or ligament defects. A further example of tissue regeneration of non-healing wounds includes pressure ulcers, ulcers associated with vascular insufficiency, surgical, and traumatic wounds.

Similarly, nerve and brain tissue could also be regenerated by using  
polynucleotides or polypeptides, as well as agonists or antagonists of the present  
25 invention, to proliferate and differentiate nerve cells. Diseases that could be treated using this method include central and peripheral nervous system diseases, neuropathies, or mechanical and traumatic disorders (e.g., spinal cord disorders, head trauma, cerebrovascular disease, and stroke). Specifically, diseases associated with peripheral nerve injuries, peripheral neuropathy (e.g., resulting from chemotherapy or  
30 other medical therapies), localized neuropathies, and central nervous system diseases

(e.g., Alzheimer's disease, Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis, and Shy-Drager syndrome), could all be treated using the polynucleotides or polypeptides, as well as agonists or antagonists of the present invention.

5

### **Chemotaxis**

Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention may have chemotaxis activity. A chemotactic molecule attracts or mobilizes cells (e.g., monocytes, fibroblasts, neutrophils, T-cells, mast cells, eosinophils, epithelial and/or endothelial cells) to a particular site in the body, such as inflammation, infection, or site of hyperproliferation. The mobilized cells can then fight off and/or heal the particular trauma or abnormality.

Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention may increase chemotactic activity of particular cells. These chemotactic molecules can then be used to treat inflammation, infection, hyperproliferative disorders, or any immune system disorder by increasing the number of cells targeted to a particular location in the body. For example, chemotactic molecules can be used to treat wounds and other trauma to tissues by attracting immune cells to the injured location. Chemotactic molecules of the present invention can also attract fibroblasts, which can be used to treat wounds.

It is also contemplated that polynucleotides or polypeptides, as well as agonists or antagonists of the present invention may inhibit chemotactic activity. These molecules could also be used to treat disorders. Thus, polynucleotides or polypeptides, as well as agonists or antagonists of the present invention could be used as an inhibitor of chemotaxis.

25

### **Binding Activity**

A polypeptide of the present invention may be used to screen for molecules that bind to the polypeptide or for molecules to which the polypeptide binds. The binding of the polypeptide and the molecule may activate (agonist), increase, inhibit

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(antagonist), or decrease activity of the polypeptide or the molecule bound. Examples of such molecules include antibodies, oligonucleotides, proteins (e.g., receptors), or small molecules.

Preferably, the molecule is closely related to the natural ligand of the polypeptide, e.g., a fragment of the ligand, or a natural substrate, a ligand, a structural or functional mimetic. (See, Coligan et al., Current Protocols in Immunology 1(2):Chapter 5 (1991).) Similarly, the molecule can be closely related to the natural receptor to which the polypeptide binds, or at least, a fragment of the receptor capable of being bound by the polypeptide (e.g., active site). In either case, the molecule can be rationally designed using known techniques.

Preferably, the screening for these molecules involves producing appropriate cells which express the polypeptide. Preferred cells include cells from mammals, yeast, *Drosophila*, or *E. coli*. Cells expressing the polypeptide (or cell membrane containing the expressed polypeptide) are then preferably contacted with a test compound potentially containing the molecule to observe binding, stimulation, or inhibition of activity of either the polypeptide or the molecule.

The assay may simply test binding of a candidate compound to the polypeptide, wherein binding is detected by a label, or in an assay involving competition with a labeled competitor. Further, the assay may test whether the candidate compound results in a signal generated by binding to the polypeptide.

Alternatively, the assay can be carried out using cell-free preparations, polypeptide/molecule affixed to a solid support, chemical libraries, or natural product mixtures. The assay may also simply comprise the steps of mixing a candidate compound with a solution containing a polypeptide, measuring polypeptide/molecule activity or binding, and comparing the polypeptide/molecule activity or binding to a standard.

Preferably, an ELISA assay can measure polypeptide level or activity in a sample (e.g., biological sample) using a monoclonal or polyclonal antibody. The antibody can measure polypeptide level or activity by either binding, directly or indirectly, to the polypeptide or by competing with the polypeptide for a substrate.

Additionally, the receptor to which the polypeptide of the present invention binds can be identified by numerous methods known to those of skill in the art, for example, ligand panning and FACS sorting (Coligan, et al., Current Protocols in Immun., 1(2), Chapter 5, (1991)). For example, expression cloning is employed  
5 wherein polyadenylated RNA is prepared from a cell responsive to the polypeptides, for example, NIH3T3 cells which are known to contain multiple receptors for the FGF family proteins, and SC-3 cells, and a cDNA library created from this RNA is divided into pools and used to transfect COS cells or other cells that are not responsive to the polypeptides. Transfected cells which are grown on glass slides are  
10 exposed to the polypeptide of the present invention, after they have been labelled. The polypeptides can be labeled by a variety of means including iodination or inclusion of a recognition site for a site-specific protein kinase.

Following fixation and incubation, the slides are subjected to autoradiographic analysis. Positive pools are identified and sub-pools are prepared and  
15 re-transfected using an iterative sub-pooling and re-screening process, eventually yielding a single clones that encodes the putative receptor.

As an alternative approach for receptor identification, the labeled polypeptides can be photoaffinity linked with cell membrane or extract preparations that express the receptor molecule. Cross-linked material is resolved by PAGE analysis and  
20 exposed to X-ray film. The labeled complex containing the receptors of the polypeptides can be excised, resolved into peptide fragments, and subjected to protein microsequencing. The amino acid sequence obtained from microsequencing would be used to design a set of degenerate oligonucleotide probes to screen a cDNA library to identify the genes encoding the putative receptors.

25 Moreover, the techniques of gene-shuffling, motif-shuffling, exon-shuffling, and/or codon-shuffling (collectively referred to as "DNA shuffling") may be employed to modulate the activities of the polypeptide of the present invention thereby effectively generating agonists and antagonists of the polypeptide of the present invention. *See generally*, U.S. Patent Nos. 5,605,793, 5,811,238, 5,830,721,  
30 5,834,252, and 5,837,458, and Patten, P. A., et al., *Curr. Opinion Biotechnol.* 8:724-

33 (1997); Harayama, S. *Trends Biotechnol.* 16(2):76-82 (1998); Hansson, L. O., *et al.*, *J. Mol. Biol.* 287:265-76 (1999); and Lorenzo, M. M. and Blasco, R. *Biotechniques* 24(2):308-13 (1998) (each of these patents and publications are hereby incorporated by reference). In one embodiment, alteration of polynucleotides and corresponding polypeptides may be achieved by DNA shuffling. DNA shuffling involves the assembly of two or more DNA segments into a desired molecule by homologous, or site-specific, recombination. In another embodiment, polynucleotides and corresponding polypeptides may be altered by being subjected to random mutagenesis by error-prone PCR, random nucleotide insertion or other methods prior to recombination. In another embodiment, one or more components, motifs, sections, parts, domains, fragments, etc., of the polypeptide of the present invention may be recombined with one or more components, motifs, sections, parts, domains, fragments, etc. of one or more heterologous molecules. In preferred embodiments, the heterologous molecules are family members. In further preferred embodiments, the heterologous molecule is a growth factor such as, for example, platelet-derived growth factor (PDGF), insulin-like growth factor (IGF-I), transforming growth factor (TGF)-alpha, epidermal growth factor (EGF), fibroblast growth factor (FGF), TGF-beta, bone morphogenetic protein (BMP)-2, BMP-4, BMP-5, BMP-6, BMP-7, activins A and B, decapentaplegic(dpp), 60A, OP-2, dorsalin, growth differentiation factors (GDFs), nodal, MIS, inhibin-alpha, TGF-beta1, TGF-beta2, TGF-beta3, TGF-beta5, and glial-derived neurotrophic factor (GDNF).

Other preferred fragments are biologically active fragments of the polypeptide of the present invention. Biologically active fragments are those exhibiting activity similar, but not necessarily identical, to an activity of the polypeptide of the present invention. The biological activity of the fragments may include an improved desired activity, or a decreased undesirable activity.

Additionally, this invention provides a method of screening compounds to identify those which modulate the action of the polypeptide of the present invention. An example of such an assay comprises combining a mammalian fibroblast cell, a the polypeptide of the present invention, the compound to be screened and  $^3\text{[H]}$

thymidine under cell culture conditions where the fibroblast cell would normally proliferate. A control assay may be performed in the absence of the compound to be screened and compared to the amount of fibroblast proliferation in the presence of the compound to determine if the compound stimulates proliferation by determining the uptake of  $^3\text{[H]}$  thymidine in each case. The amount of fibroblast cell proliferation is measured by liquid scintillation chromatography which measures the incorporation of  $^3\text{[H]}$  thymidine. Both agonist and antagonist compounds may be identified by this procedure.

In another method, a mammalian cell or membrane preparation expressing a receptor for a polypeptide of the present invention is incubated with a labeled polypeptide of the present invention in the presence of the compound. The ability of the compound to enhance or block this interaction could then be measured. Alternatively, the response of a known second messenger system following interaction of a compound to be screened and the receptor is measured and the ability of the compound to bind to the receptor and elicit a second messenger response is measured to determine if the compound is a potential agonist or antagonist. Such second messenger systems include but are not limited to, cAMP guanylate cyclase, ion channels or phosphoinositide hydrolysis.

All of these above assays can be used as diagnostic or prognostic markers. The molecules discovered using these assays can be used to treat disease or to bring about a particular result in a patient (e.g., blood vessel growth) by activating or inhibiting the polypeptide/molecule. Moreover, the assays can discover agents which may inhibit or enhance the production of the polypeptides of the invention from suitably manipulated cells or tissues.

Therefore, the invention includes a method of identifying compounds which bind to a polypeptide of the invention comprising the steps of: (a) incubating a candidate binding compound with a polypeptide of the present invention; and (b) determining if binding has occurred. Moreover, the invention includes a method of identifying agonists/antagonists comprising the steps of: (a) incubating a candidate compound with a polypeptide of the present invention, (b) assaying a biological

activity, and (b) determining if a biological activity of the polypeptide has been altered.

### **Targeted Delivery**

5           In another embodiment, the invention provides a method of delivering compositions to targeted cells expressing a receptor for a polypeptide of the invention, or cells expressing a cell bound form of a polypeptide of the invention.

          As discussed herein, polypeptides or antibodies of the invention may be associated with heterologous polypeptides, heterologous nucleic acids, toxins, or  
10   prodrugs via hydrophobic, hydrophilic, ionic and/or covalent interactions. In one embodiment, the invention provides a method for the specific delivery of compositions of the invention to cells by administering polypeptides of the invention (including antibodies) that are associated with heterologous polypeptides or nucleic acids. In one example, the invention provides a method for delivering a therapeutic  
15   protein into the targeted cell. In another example, the invention provides a method for delivering a single stranded nucleic acid (e.g., antisense or ribozymes) or double stranded nucleic acid (e.g., DNA that can integrate into the cell's genome or replicate episomally and that can be transcribed) into the targeted cell.

          In another embodiment, the invention provides a method for the specific  
20   destruction of cells (e.g., the destruction of tumor cells) by administering polypeptides of the invention (e.g., polypeptides of the invention or antibodies of the invention) in association with toxins or cytotoxic prodrugs.

          By "toxin" is meant compounds that bind and activate endogenous cytotoxic effector systems, radioisotopes, holotoxins, modified toxins, catalytic subunits of  
25   toxins, or any molecules or enzymes not normally present in or on the surface of a cell that under defined conditions cause the cell's death. Toxins that may be used according to the methods of the invention include, but are not limited to, radioisotopes known in the art, compounds such as, for example, antibodies (or complement fixing containing portions thereof) that bind an inherent or induced  
30   endogenous cytotoxic effector system, thymidine kinase, endonuclease, RNase, alpha

toxin, ricin, abrin, *Pseudomonas* exotoxin A, diphtheria toxin, saporin, momordin, gelonin, pokeweed antiviral protein, alpha-sarcin and cholera toxin. By "cytotoxic prodrug" is meant a non-toxic compound that is converted by an enzyme, normally present in the cell, into a cytotoxic compound. Cytotoxic prodrugs that may be used according to the methods of the invention include, but are not limited to, glutamyl derivatives of benzoic acid mustard alkylating agent, phosphate derivatives of etoposide or mitomycin C, cytosine arabinoside, daunorubisin, and phenoxyacetamide derivatives of doxorubicin.

#### 10 Drug Screening

Further contemplated is the use of the polypeptides of the present invention, or the polynucleotides encoding these polypeptides, to screen for molecules which modify the activities of the polypeptides of the present invention. Such a method would include contacting the polypeptide of the present invention with a selected compound(s) suspected of having antagonist or agonist activity, and assaying the activity of these polypeptides following binding.

This invention is particularly useful for screening therapeutic compounds by using the polypeptides of the present invention, or binding fragments thereof, in any of a variety of drug screening techniques. The polypeptide or fragment employed in such a test may be affixed to a solid support, expressed on a cell surface, free in solution, or located intracellularly. One method of drug screening utilizes eukaryotic or prokaryotic host cells which are stably transformed with recombinant nucleic acids expressing the polypeptide or fragment. Drugs are screened against such transformed cells in competitive binding assays. One may measure, for example, the formulation of complexes between the agent being tested and a polypeptide of the present invention.

Thus, the present invention provides methods of screening for drugs or any other agents which affect activities mediated by the polypeptides of the present invention. These methods comprise contacting such an agent with a polypeptide of the present invention or a fragment thereof and assaying for the presence of a

complex between the agent and the polypeptide or a fragment thereof, by methods well known in the art. In such a competitive binding assay, the agents to screen are typically labeled. Following incubation, free agent is separated from that present in bound form, and the amount of free or uncomplexed label is a measure of the ability  
5 of a particular agent to bind to the polypeptides of the present invention.

Another technique for drug screening provides high throughput screening for compounds having suitable binding affinity to the polypeptides of the present invention, and is described in great detail in European Patent Application 84/03564, published on September 13, 1984, which is incorporated herein by reference herein.  
10 Briefly stated, large numbers of different small peptide test compounds are synthesized on a solid substrate, such as plastic pins or some other surface. The peptide test compounds are reacted with polypeptides of the present invention and washed. Bound polypeptides are then detected by methods well known in the art. Purified polypeptides are coated directly onto plates for use in the aforementioned  
15 drug screening techniques. In addition, non-neutralizing antibodies may be used to capture the peptide and immobilize it on the solid support.

This invention also contemplates the use of competitive drug screening assays in which neutralizing antibodies capable of binding polypeptides of the present invention specifically compete with a test compound for binding to the polypeptides  
20 or fragments thereof. In this manner, the antibodies are used to detect the presence of any peptide which shares one or more antigenic epitopes with a polypeptide of the invention.

#### **Antisense And Ribozyme (Antagonists)**

25 In specific embodiments, antagonists according to the present invention are nucleic acids corresponding to the sequences contained in SEQ ID NO:X, or the complementary strand thereof, and/or to nucleotide sequences contained in the cDNA contained in the related cDNA clone identified in Table 1. In one embodiment, antisense sequence is generated internally, by the organism, in another embodiment,  
30 the antisense sequence is separately administered (see, for example, O'Connor, J.,

Neurochem. 56:560 (1991). Oligodeoxynucleotides as Antisense Inhibitors of Gene Expression, CRC Press, Boca Raton, FL (1988). Antisense technology can be used to control gene expression through antisense DNA or RNA, or through triple-helix formation. Antisense techniques are discussed for example, in Okano, J., Neurochem. 56:560 (1991); Oligodeoxynucleotides as Antisense Inhibitors of Gene Expression, CRC Press, Boca Raton, FL (1988). Triple helix formation is discussed in, for instance, Lee et al., Nucleic Acids Research 6:3073 (1979); Cooney et al., Science 241:456 (1988); and Dervan et al., Science 251:1300 (1991). The methods are based on binding of a polynucleotide to a complementary DNA or RNA.

For example, the use of c-myc and c-myb antisense RNA constructs to inhibit the growth of the non-lymphocytic leukemia cell line HL-60 and other cell lines was previously described. (Wickstrom et al. (1988); Anfossi et al. (1989)). These experiments were performed in vitro by incubating cells with the oligoribonucleotide. A similar procedure for in vivo use is described in WO 91/15580. Briefly, a pair of oligonucleotides for a given antisense RNA is produced as follows: A sequence complimentary to the first 15 bases of the open reading frame is flanked by an EcoRI site on the 5' end and a HindIII site on the 3' end. Next, the pair of oligonucleotides is heated at 90°C for one minute and then annealed in 2X ligation buffer (20mM TRIS HCl pH 7.5, 10mM MgCl<sub>2</sub>, 10mM dithiothreitol (DTT) and 0.2 mM ATP) and then ligated to the EcoRI/Hind III site of the retroviral vector PMV7 (WO 91/15580).

For example, the 5' coding portion of a polynucleotide that encodes the polypeptide of the present invention may be used to design an antisense RNA oligonucleotide of from about 10 to 40 base pairs in length. A DNA oligonucleotide is designed to be complementary to a region of the gene involved in transcription thereby preventing transcription and the production of the receptor. The antisense RNA oligonucleotide hybridizes to the mRNA in vivo and blocks translation of the mRNA molecule into receptor polypeptide.

In one embodiment, the antisense nucleic acid of the invention is produced intracellularly by transcription from an exogenous sequence. For example, a vector or a portion thereof, is transcribed, producing an antisense nucleic acid (RNA) of the



invention. Such a vector would contain a sequence encoding the antisense nucleic acid. Such a vector can remain episomal or become chromosomally integrated, as long as it can be transcribed to produce the desired antisense RNA. Such vectors can be constructed by recombinant DNA technology methods standard in the art. Vectors  
5 can be plasmid, viral, or others known in the art, used for replication and expression in vertebrate cells. Expression of the sequence encoding the polypeptide of the present invention or fragments thereof, can be by any promoter known in the art to act in vertebrate, preferably human cells. Such promoters can be inducible or constitutive. Such promoters include, but are not limited to, the SV40 early promoter  
10 region (Bernoist and Chambon, *Nature* 29:304-310 (1981)), the promoter contained in the 3' long terminal repeat of Rous sarcoma virus (Yamamoto et al., *Cell* 22:787-797 (1980)), the herpes thymidine promoter (Wagner et al., *Proc. Natl. Acad. Sci. U.S.A.* 78:1441-1445 (1981)), the regulatory sequences of the metallothionein gene (Brinster, et al., *Nature* 296:39-42 (1982)), etc.

15 The antisense nucleic acids of the invention comprise a sequence complementary to at least a portion of an RNA transcript of a gene of the present invention. However, absolute complementarity, although preferred, is not required. A sequence "complementary to at least a portion of an RNA," referred to herein, means a sequence having sufficient complementarity to be able to hybridize with the  
20 RNA, forming a stable duplex; in the case of double stranded antisense nucleic acids, a single strand of the duplex DNA may thus be tested, or triplex formation may be assayed. The ability to hybridize will depend on both the degree of complementarity and the length of the antisense nucleic acid. Generally, the larger the hybridizing nucleic acid, the more base mismatches with a RNA it may contain and still form a  
25 stable duplex (or triplex as the case may be). One skilled in the art can ascertain a tolerable degree of mismatch by use of standard procedures to determine the melting point of the hybridized complex.

Oligonucleotides that are complementary to the 5' end of the message, e.g., the  
30 5' untranslated sequence up to and including the AUG initiation codon, should work most efficiently at inhibiting translation. However, sequences complementary to the

3' untranslated sequences of mRNAs have been shown to be effective at inhibiting translation of mRNAs as well. See generally, Wagner, R., 1994, Nature 372:333-335. Thus, oligonucleotides complementary to either the 5'- or 3'- non- translated, non-coding regions of polynucleotide sequences described herein could be used in an antisense approach to inhibit translation of endogenous mRNA. Oligonucleotides complementary to the 5' untranslated region of the mRNA should include the complement of the AUG start codon. Antisense oligonucleotides complementary to mRNA coding regions are less efficient inhibitors of translation but could be used in accordance with the invention. Whether designed to hybridize to the 5'-, 3'- or coding region of mRNA of the present invention, antisense nucleic acids should be at least six nucleotides in length, and are preferably oligonucleotides ranging from 6 to about 50 nucleotides in length. In specific aspects the oligonucleotide is at least 10 nucleotides, at least 17 nucleotides, at least 25 nucleotides or at least 50 nucleotides.

The polynucleotides of the invention can be DNA or RNA or chimeric mixtures or derivatives or modified versions thereof, single-stranded or double-stranded. The oligonucleotide can be modified at the base moiety, sugar moiety, or phosphate backbone, for example, to improve stability of the molecule, hybridization, etc. The oligonucleotide may include other appended groups such as peptides (e.g., for targeting host cell receptors in vivo), or agents facilitating transport across the cell membrane (see, e.g., Letsinger et al., 1989, Proc. Natl. Acad. Sci. U.S.A. 86:6553-6556; Lemaitre et al., 1987, Proc. Natl. Acad. Sci. 84:648-652; PCT Publication No. WO88/09810, published December 15, 1988) or the blood-brain barrier (see, e.g., PCT Publication No. WO89/10134, published April 25, 1988), hybridization-triggered cleavage agents. (See, e.g., Krol et al., 1988, BioTechniques 6:958-976) or intercalating agents. (See, e.g., Zon, 1988, Pharm. Res. 5:539-549). To this end, the oligonucleotide may be conjugated to another molecule, e.g., a peptide, hybridization triggered cross-linking agent, transport agent, hybridization-triggered cleavage agent, etc.

The antisense oligonucleotide may comprise at least one modified base moiety which is selected from the group including, but not limited to, 5-fluorouracil,

5-bromouracil, 5-chlorouracil, 5-iodouracil, hypoxanthine, xantine, 4-acetylcytosine, 5-(carboxyhydroxymethyl) uracil, 5-carboxymethylaminomethyl-2-thiouridine, 5-carboxymethylaminomethyluracil, dihydrouracil, beta-D-galactosylqueosine, inosine, N6-isopentenyladenine, 1-methylguanine, 1-methylinosine, 5 2,2-dimethylguanine, 2-methyladenine, 2-methylguanine, 3-methylcytosine, 5-methylcytosine, N6-adenine, 7-methylguanine, 5-methylaminomethyluracil, 5-methoxyaminomethyl-2-thiouracil, beta-D-mannosylqueosine, 5'-methoxycarboxymethyluracil, 5-methoxyuracil, 2-methylthio-N6-isopentenyladenine, uracil-5-oxyacetic acid (v), wybutoxosine, pseudouracil, 10 queosine, 2-thiocytosine, 5-methyl-2-thiouracil, 2-thiouracil, 4-thiouracil, 5-methyluracil, uracil-5-oxyacetic acid methylester, uracil-5-oxyacetic acid (v), 5-methyl-2-thiouracil, 3-(3-amino-3-N-2-carboxypropyl) uracil, (acp3)w, and 2,6-diaminopurine.

The antisense oligonucleotide may also comprise at least one modified sugar 15 moiety selected from the group including, but not limited to, arabinose, 2-fluoroarabinose, xylulose, and hexose.

In yet another embodiment, the antisense oligonucleotide comprises at least one modified phosphate backbone selected from the group including, but not limited to, a phosphorothioate, a phosphorodithioate, a phosphoramidothioate, a 20 phosphoramidate, a phosphordiamidate, a methylphosphonate, an alkyl phosphotriester, and a formacetal or analog thereof.

In yet another embodiment, the antisense oligonucleotide is an a-anomeric oligonucleotide. An a-anomeric oligonucleotide forms specific double-stranded hybrids with complementary RNA in which, contrary to the usual b-units, the strands 25 run parallel to each other (Gautier et al., 1987, Nucl. Acids Res. 15:6625-6641). The oligonucleotide is a 2'-O-methylribonucleotide (Inoue et al., 1987, Nucl. Acids Res. 15:6131-6148), or a chimeric RNA-DNA analogue (Inoue et al., 1987, FEBS Lett. 215:327-330).

Polynucleotides of the invention may be synthesized by standard methods 30 known in the art, e.g. by use of an automated DNA synthesizer (such as are

commercially available from Biosearch, Applied Biosystems, etc.). As examples, phosphorothioate oligonucleotides may be synthesized by the method of Stein et al. (1988, Nucl. Acids Res. 16:3209), methylphosphonate oligonucleotides can be prepared by use of controlled pore glass polymer supports (Sarin et al., 1988, Proc. Natl. Acad. Sci. U.S.A. 85:7448-7451), etc.

While antisense nucleotides complementary to the coding region sequence could be used, those complementary to the transcribed untranslated region are most preferred.

Potential antagonists according to the invention also include catalytic RNA, or a ribozyme (See, e.g., PCT International Publication WO 90/11364, published October 4, 1990; Sarver et al, Science 247:1222-1225 (1990). While ribozymes that cleave mRNA at site specific recognition sequences can be used to destroy mRNAs, the use of hammerhead ribozymes is preferred. Hammerhead ribozymes cleave mRNAs at locations dictated by flanking regions that form complementary base pairs with the target mRNA. The sole requirement is that the target mRNA have the following sequence of two bases: 5'-UG-3'. The construction and production of hammerhead ribozymes is well known in the art and is described more fully in Haseloff and Gerlach, Nature 334:585-591 (1988). There are numerous potential hammerhead ribozyme cleavage sites within the nucleotide sequence of SEQ ID NO:X. Preferably, the ribozyme is engineered so that the cleavage recognition site is located near the 5' end of the mRNA; i.e., to increase efficiency and minimize the intracellular accumulation of non-functional mRNA transcripts.

As in the antisense approach, the ribozymes of the invention can be composed of modified oligonucleotides (e.g. for improved stability, targeting, etc.) and should be delivered to cells which express in vivo. DNA constructs encoding the ribozyme may be introduced into the cell in the same manner as described above for the introduction of antisense encoding DNA. A preferred method of delivery involves using a DNA construct "encoding" the ribozyme under the control of a strong constitutive promoter, such as, for example, pol III or pol II promoter, so that transfected cells will produce sufficient quantities of the ribozyme to destroy

endogenous messages and inhibit translation. Since ribozymes unlike antisense molecules, are catalytic, a lower intracellular concentration is required for efficiency.

Antagonist/agonist compounds may be employed to inhibit the cell growth and proliferation effects of the polypeptides of the present invention on neoplastic  
5 cells and tissues, i.e. stimulation of angiogenesis of tumors, and, therefore, retard or prevent abnormal cellular growth and proliferation, for example, in tumor formation or growth.

The antagonist/agonist may also be employed to prevent hyper-vascular diseases, and prevent the proliferation of epithelial lens cells after extracapsular  
10 cataract surgery. Prevention of the mitogenic activity of the polypeptides of the present invention may also be desirable in cases such as restenosis after balloon angioplasty.

The antagonist/agonist may also be employed to prevent the growth of scar tissue during wound healing.

15 The antagonist/agonist may also be employed to treat the diseases described herein.

Thus, the invention provides a method of treating disorders or diseases, including but not limited to the disorders or diseases listed throughout this application, associated with overexpression of a polynucleotide of the present  
20 invention by administering to a patient (a) an antisense molecule directed to the polynucleotide of the present invention, and/or (b) a ribozyme directed to the polynucleotide of the present invention.

#### **Other Activities**

25 A polypeptide, polynucleotide, agonist, or antagonist of the present invention, as a result of the ability to stimulate vascular endothelial cell growth, may be employed in treatment for stimulating re-vascularization of ischemic tissues due to various disease conditions such as thrombosis, arteriosclerosis, and other cardiovascular conditions. The polypeptide, polynucleotide, agonist, or antagonist of

the present invention may also be employed to stimulate angiogenesis and limb regeneration, as discussed above.

5 A polypeptide, polynucleotide, agonist, or antagonist of the present invention may also be employed for treating wounds due to injuries, burns, post-operative tissue repair, and ulcers since they are mitogenic to various cells of different origins, such as fibroblast cells and skeletal muscle cells, and therefore, facilitate the repair or replacement of damaged or diseased tissue.

10 A polypeptide, polynucleotide, agonist, or antagonist of the present invention may also be employed stimulate neuronal growth and to treat and prevent neuronal damage which occurs in certain neuronal disorders or neuro-degenerative conditions such as Alzheimer's disease, Parkinson's disease, and AIDS-related complex. A polypeptide, polynucleotide, agonist, or antagonist of the present invention may have the ability to stimulate chondrocyte growth, therefore, they may be employed to enhance bone and periodontal regeneration and aid in tissue transplants or bone  
15 grafts.

A polypeptide, polynucleotide, agonist, or antagonist of the present invention may be also be employed to prevent skin aging due to sunburn by stimulating keratinocyte growth.

20 A polypeptide, polynucleotide, agonist, or antagonist of the present invention may also be employed for preventing hair loss, since FGF family members activate hair-forming cells and promotes melanocyte growth. Along the same lines, a polypeptide, polynucleotide, agonist, or antagonist of the present invention may be employed to stimulate growth and differentiation of hematopoietic cells and bone marrow cells when used in combination with other cytokines.

25 A polypeptide, polynucleotide, agonist, or antagonist of the present invention may also be employed to maintain organs before transplantation or for supporting cell culture of primary tissues. A polypeptide, polynucleotide, agonist, or antagonist of the present invention may also be employed for inducing tissue of mesodermal origin to differentiate in early embryos.

A polypeptide, polynucleotide, agonist, or antagonist of the present invention may also increase or decrease the differentiation or proliferation of embryonic stem cells, besides, as discussed above, hematopoietic lineage.

5 A polypeptide, polynucleotide, agonist, or antagonist of the present invention may also be used to modulate mammalian characteristics, such as body height, weight, hair color, eye color, skin, percentage of adipose tissue, pigmentation, size, and shape (e.g., cosmetic surgery). Similarly, a polypeptide, polynucleotide, agonist, or antagonist of the present invention may be used to modulate mammalian metabolism affecting catabolism, anabolism, processing, utilization, and storage of  
10 energy.

A polypeptide, polynucleotide, agonist, or antagonist of the present invention may be used to change a mammal's mental state or physical state by influencing biorhythms, circadian rhythms, depression (including depressive disorders), tendency for violence, tolerance for pain, reproductive capabilities (preferably by Activin or  
15 Inhibin-like activity), hormonal or endocrine levels, appetite, libido, memory, stress, or other cognitive qualities.

A polypeptide, polynucleotide, agonist, or antagonist of the present invention may also be used as a food additive or preservative, such as to increase or decrease storage capabilities, fat content, lipid, protein, carbohydrate, vitamins, minerals,  
20 cofactors or other nutritional components.

The above-recited applications have uses in a wide variety of hosts. Such hosts include, but are not limited to, human, murine, rabbit, goat, guinea pig, camel, horse, mouse, rat, hamster, pig, micro-pig, chicken, goat, cow, sheep, dog, cat, non-human primate, and human. In specific embodiments, the host is a mouse, rabbit,  
25 goat, guinea pig, chicken, rat, hamster, pig, sheep, dog or cat. In preferred embodiments, the host is a mammal. In most preferred embodiments, the host is a human.

#### **Other Preferred Embodiments**

Other preferred embodiments of the claimed invention include an isolated nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to a sequence of at least about 50 contiguous nucleotides in the nucleotide sequence of SEQ ID NO:X or the complementary strand thereto, and/or the cDNA in the related cDNA clone contained in the deposit.

Also preferred is a nucleic acid molecule wherein said sequence of contiguous nucleotides is included in the nucleotide sequence of SEQ ID NO:X in the range of positions identified as "Start" and "End" in columns 7 and 8 as defined for SEQ ID NO:X in Table 1.

Also preferred is an isolated nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to a sequence of at least about 150 contiguous nucleotides in the nucleotide sequence of SEQ ID NO:X or the complementary strand thereto, and/or the cDNA in the related cDNA clone contained in the deposit.

Further preferred is an isolated nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to a sequence of at least about 500 contiguous nucleotides in the nucleotide sequence of SEQ ID NO:X or the complementary strand thereto, and/or the cDNA in the related cDNA clone contained in the deposit.

A further preferred embodiment is a nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to the nucleotide sequence of SEQ ID NO:X in the range of positions identified as "Start" and "End" in columns 7 and 8 as defined for SEQ ID NO:X in Table 1.

A further preferred embodiment is an isolated nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to the complete nucleotide sequence of SEQ ID NO:X or the complementary strand thereto, and/or the cDNA in the related cDNA clone contained in the deposit.

Also preferred is an isolated nucleic acid molecule which hybridizes under stringent hybridization conditions to a nucleic acid molecule comprising a nucleotide sequence of SEQ ID NO:X or the complementary strand thereto, and/or the cDNA in



the related cDNA clone contained in the deposit, wherein said nucleic acid molecule which hybridizes does not hybridize under stringent hybridization conditions to a nucleic acid molecule having a nucleotide sequence consisting of only A residues or of only T residues.

5 Also preferred is a composition of matter comprising a DNA molecule which comprises a cDNA clone contained in the deposit.

Also preferred is an isolated nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to a sequence of at least 50 contiguous nucleotides in the nucleotide sequence of the cDNA in the related cDNA clone  
10 contained in the deposit.

Also preferred is an isolated nucleic acid molecule, wherein said sequence of at least 50 contiguous nucleotides is included in the nucleotide sequence of an open reading frame sequence encoded by the cDNA in the related cDNA clone contained in the deposit.

15 Also preferred is an isolated nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to sequence of at least 150 contiguous nucleotides in the nucleotide sequence encoded by the cDNA in the related cDNA clone contained in the deposit.

A further preferred embodiment is an isolated nucleic acid molecule  
20 comprising a nucleotide sequence which is at least 95% identical to sequence of at least 500 contiguous nucleotides in the nucleotide sequence encoded by the cDNA in the related cDNA clone contained in the deposit.

A further preferred embodiment is an isolated nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to the complete  
25 nucleotide sequence encoded by the cDNA in the related cDNA clone contained in the deposit.

A further preferred embodiment is a method for detecting in a biological sample a nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to a sequence of at least 50 contiguous nucleotides in a sequence  
30 selected from the group consisting of: a nucleotide sequence of SEQ ID NO:X or the

complementary strand thereto; and a nucleotide sequence encoded by the cDNA in the related cDNA clone contained in the deposit; which method comprises a step of comparing a nucleotide sequence of at least one nucleic acid molecule in said sample with a sequence selected from said group and determining whether the sequence of  
5 said nucleic acid molecule in said sample is at least 95% identical to said selected sequence.

Also preferred is the above method wherein said step of comparing sequences comprises determining the extent of nucleic acid hybridization between nucleic acid molecules in said sample and a nucleic acid molecule comprising said sequence  
10 selected from said group. Similarly, also preferred is the above method wherein said step of comparing sequences is performed by comparing the nucleotide sequence determined from a nucleic acid molecule in said sample with said sequence selected from said group. The nucleic acid molecules can comprise DNA molecules or RNA molecules.

15 A further preferred embodiment is a method for identifying the species, tissue or cell type of a biological sample which method comprises a step of detecting nucleic acid molecules in said sample, if any, comprising a nucleotide sequence that is at least 95% identical to a sequence of at least 50 contiguous nucleotides in a sequence selected from the group consisting of: a nucleotide sequence of SEQ ID NO:X or the  
20 complementary strand thereto; and a nucleotide sequence encoded by the cDNA in the related cDNA clone contained in the deposit.

Also preferred is the above method for identifying the species, tissue or cell type of a biological sample which comprises a step of detecting nucleic acid molecules comprising a nucleotide sequence in a panel of at least two nucleotide  
25 sequences, wherein at least one sequence in said panel is at least 95% identical to a sequence of at least 50 contiguous nucleotides in a sequence selected from said group.

Also preferred is a method for diagnosing in a subject a pathological condition associated with abnormal structure or expression of a nucleotide sequence of SEQ ID NO:X; or the cDNA in the related cDNA clone identified in Table 1 which encodes a  
30 protein, wherein the method comprises a step of detecting in a biological sample

obtained from said subject nucleic acid molecules, if any, comprising a nucleotide sequence that is at least 95% identical to a sequence of at least 50 contiguous nucleotides in a sequence selected from the group consisting of: a nucleotide sequence of SEQ ID NO:X or the complementary strand thereto; and a nucleotide  
5 sequence of the cDNA in the related cDNA clone contained in the deposit.

Also preferred is the above method for diagnosing a pathological condition which comprises a step of detecting nucleic acid molecules comprising a nucleotide sequence in a panel of at least two nucleotide sequences, wherein at least one sequence in said panel is at least 95% identical to a sequence of at least 50 contiguous  
10 nucleotides in a sequence selected from said group.

Also preferred is a composition of matter comprising isolated nucleic acid molecules wherein the nucleotide sequences of said nucleic acid molecules comprise a panel of at least two nucleotide sequences, wherein at least one sequence in said panel is at least 95% identical to a sequence of at least 50 contiguous nucleotides in a  
15 sequence selected from the group consisting of: a nucleotide sequence of SEQ ID NO:X or the complementary strand thereto; and a nucleotide sequence encoded by the cDNA in the related cDNA clone contained in the deposit. The nucleic acid molecules can comprise DNA molecules or RNA molecules.

Also preferred is a composition of matter comprising isolated nucleic acid  
20 molecules wherein the nucleotide sequences of said nucleic acid molecules comprise a DNA microarray or "chip" of at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25, 30, 40, 50, 100, 150, 200, 250, 300, 500, 1000, 2000, 3000 or 4000 nucleotide sequences, wherein at least one sequence in said DNA microarray or "chip" is at least 95% identical to a sequence of at least 50 contiguous nucleotides in a sequence selected  
25 from the group consisting of: a nucleotide sequence of SEQ ID NO:X or the complementary strand thereto; and a nucleotide sequence encoded by the cDNA in the cDNA clone referenced in Table 1. The nucleic acid molecules can comprise DNA molecules or RNA molecules.

Also preferred is an isolated polypeptide comprising an amino acid sequence  
30 at least 90% identical to a sequence of at least about 10 contiguous amino acids in the

polypeptide sequence of SEQ ID NO:Y; a polypeptide encoded by SEQ ID NO:X; and/or a polypeptide encoded by the cDNA in the related cDNA clone contained in the deposit.

Also preferred is an isolated polypeptide comprising an amino acid sequence  
5 at least 95% identical to a sequence of at least about 30 contiguous amino acids in the amino acid sequence of SEQ ID NO:Y; a polypeptide encoded by SEQ ID NO:X; and/or a polypeptide encoded by the cDNA in the related cDNA clone contained in the deposit.

Further preferred is an isolated polypeptide comprising an amino acid  
10 sequence at least 95% identical to a sequence of at least about 100 contiguous amino acids in the amino acid sequence of SEQ ID NO:Y; a polypeptide encoded by SEQ ID NO:X; and/or a polypeptide encoded by the cDNA in the related cDNA clone contained in the deposit.

Further preferred is an isolated polypeptide comprising an amino acid  
15 sequence at least 95% identical to the complete amino acid sequence of SEQ ID NO:Y; a polypeptide encoded by SEQ ID NO:X; and/or a polypeptide encoded by the cDNA in the related cDNA clone contained in the deposit.

Further preferred is an isolated polypeptide comprising an amino acid  
20 sequence at least 90% identical to a sequence of at least about 10 contiguous amino acids in the complete amino acid sequence of a polypeptide encoded by the cDNA clone referenced in Table 1.

Also preferred is a polypeptide wherein said sequence of contiguous amino  
acids is included in the amino acid sequence of a portion of said polypeptide encoded by the cDNA clone referenced in Table 1; a polypeptide encoded by SEQ ID NO:X;  
25 and/or the polypeptide sequence of SEQ ID NO:Y.

Also preferred is an isolated polypeptide comprising an amino acid sequence at least 95% identical to a sequence of at least about 30 contiguous amino acids in the amino acid sequence of a polypeptide encoded by the cDNA clone referenced in Table 1.

Also preferred is an isolated polypeptide comprising an amino acid sequence at least 95% identical to a sequence of at least about 100 contiguous amino acids in the amino acid sequence of a polypeptide encoded by the cDNA clone referenced in Table 1.

5 Also preferred is an isolated polypeptide comprising an amino acid sequence at least 95% identical to the amino acid sequence of a polypeptide encoded by the cDNA clone referenced in Table 1.

Further preferred is an isolated antibody which binds specifically to a polypeptide comprising an amino acid sequence that is at least 90% identical to a  
10 sequence of at least 10 contiguous amino acids in a sequence selected from the group consisting of: a polypeptide sequence of SEQ ID NO:Y; a polypeptide encoded by SEQ ID NO:X; and a polypeptide encoded by the cDNA in the related cDNA clone contained in the deposit.

Further preferred is a method for detecting in a biological sample a  
15 polypeptide comprising an amino acid sequence which is at least 90% identical to a sequence of at least 10 contiguous amino acids in a sequence selected from the group consisting of: a polypeptide sequence of SEQ ID NO:Y; a polypeptide encoded by SEQ ID NO:X; and a polypeptide encoded by the cDNA in the related cDNA clone referenced in Table 1; which method comprises a step of comparing an amino acid  
20 sequence of at least one polypeptide molecule in said sample with a sequence selected from said group and determining whether the sequence of said polypeptide molecule in said sample is at least 90% identical to said sequence of at least 10 contiguous amino acids.

Also preferred is the above method wherein said step of comparing an amino  
25 acid sequence of at least one polypeptide molecule in said sample with a sequence selected from said group comprises determining the extent of specific binding of polypeptides in said sample to an antibody which binds specifically to a polypeptide comprising an amino acid sequence that is at least 90% identical to a sequence of at least 10 contiguous amino acids in a sequence selected from the group consisting of: a  
30 polypeptide sequence of SEQ ID NO:Y; a polypeptide encoded by SEQ ID NO:X;

and a polypeptide encoded by the cDNA in the related cDNA clone referenced in Table 1.

Also preferred is the above method wherein said step of comparing sequences is performed by comparing the amino acid sequence determined from a polypeptide molecule in said sample with said sequence selected from said group.

Also preferred is a method for identifying the species, tissue or cell type of a biological sample which method comprises a step of detecting polypeptide molecules in said sample, if any, comprising an amino acid sequence that is at least 90% identical to a sequence of at least 10 contiguous amino acids in a sequence selected from the group consisting of: polypeptide sequence of SEQ ID NO:Y; a polypeptide encoded by SEQ ID NO:X; and a polypeptide encoded by the cDNA in the related cDNA clone referenced in Table 1.

Also preferred is the above method for identifying the species, tissue or cell type of a biological sample, which method comprises a step of detecting polypeptide molecules comprising an amino acid sequence in a panel of at least two amino acid sequences, wherein at least one sequence in said panel is at least 90% identical to a sequence of at least 10 contiguous amino acids in a sequence selected from the above group.

Also preferred is a method for diagnosing in a subject a pathological condition associated with abnormal structure or expression of a nucleic acid sequence identified in Table 1 encoding a polypeptide, which method comprises a step of detecting in a biological sample obtained from said subject polypeptide molecules comprising an amino acid sequence in a panel of at least two amino acid sequences, wherein at least one sequence in said panel is at least 90% identical to a sequence of at least 10 contiguous amino acids in a sequence selected from the group consisting of: polypeptide sequence of SEQ ID NO:Y; a polypeptide encoded by SEQ ID NO:X; and a polypeptide encoded by the cDNA in the related cDNA clone referenced in Table 1.

In any of these methods, the step of detecting said polypeptide molecules includes using an antibody.

Also preferred is an isolated nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to a nucleotide sequence encoding a polypeptide wherein said polypeptide comprises an amino acid sequence that is at least 90% identical to a sequence of at least 10 contiguous amino acids in a sequence  
5 selected from the group consisting of: polypeptide sequence of SEQ ID NO:Y; a polypeptide encoded by SEQ ID NO:X; and a polypeptide encoded by the cDNA in the related cDNA clone referenced in Table 1.

Also preferred is an isolated nucleic acid molecule, wherein said nucleotide sequence encoding a polypeptide has been optimized for expression of said  
10 polypeptide in a prokaryotic host.

Also preferred is an isolated nucleic acid molecule, wherein said polypeptide comprises an amino acid sequence selected from the group consisting of: polypeptide sequence of SEQ ID NO:Y; a polypeptide encoded by SEQ ID NO:X; and a polypeptide encoded by the cDNA in the related cDNA clone referenced in Table 1.

15 Further preferred is a method of making a recombinant vector comprising inserting any of the above isolated nucleic acid molecule into a vector. Also preferred is the recombinant vector produced by this method. Also preferred is a method of making a recombinant host cell comprising introducing the vector into a host cell, as well as the recombinant host cell produced by this method.

20 Also preferred is a method of making an isolated polypeptide comprising culturing this recombinant host cell under conditions such that said polypeptide is expressed and recovering said polypeptide. Also preferred is this method of making an isolated polypeptide, wherein said recombinant host cell is a eukaryotic cell and said polypeptide is a human protein comprising an amino acid sequence selected from  
25 the group consisting of: polypeptide sequence of SEQ ID NO:Y; a polypeptide encoded by SEQ ID NO:X; and a polypeptide encoded by the cDNA in the related cDNA clone referenced in Table 1. The isolated polypeptide produced by this method is also preferred.

Also preferred is a method of treatment of an individual in need of an  
30 increased level of a protein activity, which method comprises administering to such

an individual a Therapeutic comprising an amount of an isolated polypeptide, polynucleotide, immunogenic fragment or analogue thereof, binding agent, antibody, or antigen binding fragment of the claimed invention effective to increase the level of said protein activity in said individual.

- 5           Also preferred is a method of treatment of an individual in need of a decreased level of a protein activity, which method comprised administering to such an individual a Therapeutic comprising an amount of an isolated polypeptide, polynucleotide, immunogenic fragment or analogue thereof, binding agent, antibody, or antigen binding fragment of the claimed invention effective to decrease the level of
- 10   said protein activity in said individual.

          Having generally described the invention, the same will be more readily understood by reference to the following examples, which are provided by way of illustration and are not intended as limiting.



*Examples**Example 1: Isolation of a Selected cDNA Clone From the Deposited Sample*

5 Each deposited cDNA clone is contained in a plasmid vector. Table 5 identifies the vectors used to construct the cDNA library from which each clone was isolated. In many cases, the vector used to construct the library is a phage vector from which a plasmid has been excised. The following correlates the related plasmid for each phage vector used in constructing the cDNA library. For example, where a  
 10 particular clone is identified in Table 5 as being isolated in the vector "Lambda Zap," the corresponding deposited clone is in "pBluescript."

	<u>Vector Used to Construct Library</u>	<u>Corresponding Deposited Plasmid</u>
	Lambda Zap	pBluescript (pBS)
	Uni-Zap XR	pBluescript (pBS)
15	Zap Express	pBK
	lafmid BA	plafmid BA
	pSport1	pSport1
	pCMVSPORT 2.0	pCMVSPORT 2.0
	pCMVSPORT 3.0	pCMVSPORT 3.0
20	pCR <sup>®</sup> 2.1	pCR <sup>®</sup> 2.1

Vectors Lambda Zap (U.S. Patent Nos. 5,128,256 and 5,286,636), Uni-Zap XR (U.S. Patent Nos. 5,128,256 and 5,286,636), Zap Express (U.S. Patent Nos. 5,128,256 and 5,286,636), pBluescript (pBS) (Short, J. M. et al., Nucleic Acids Res. 16:7583-7600 (1988); Alting-Mees, M. A. and Short, J. M., Nucleic Acids Res. 25 17:9494 (1989)) and pBK (Alting-Mees, M. A. et al., Strategies 5:58-61 (1992)) are commercially available from Stratagene Cloning Systems, Inc., 11011 N. Torrey Pines Road, La Jolla, CA, 92037. pBS contains an ampicillin resistance gene and pBK contains a neomycin resistance gene. Both can be transformed into E. coli strain XL-1 Blue, also available from Stratagene. pBS comes in 4 forms SK<sup>+</sup>, SK<sup>-</sup>, KS<sup>+</sup> and KS. The S and K refers to the orientation of the polylinker to the T7 and T3  
 30

primer sequences which flank the polylinker region ("S" is for SacI and "K" is for KpnI which are the first sites on each respective end of the linker). "+" or "-" refer to the orientation of the fl origin of replication ("ori"), such that in one orientation, single stranded rescue initiated from the fl ori generates sense strand DNA and in the other, antisense.

Vectors pSport1, pCMVSPORT 2.0 and pCMVSPORT 3.0, were obtained from Life Technologies, Inc., P. O. Box 6009, Gaithersburg, MD 20897. All Sport vectors contain an ampicillin resistance gene and may be transformed into E. coli strain DH10B, also available from Life Technologies. (See, for instance, Gruber, C. E., et al., Focus 15:59 (1993).) Vector lacmid BA (Bento Soares, Columbia University, NY) contains an ampicillin resistance gene and can be transformed into E. coli strain XL-1 Blue. Vector pCR<sup>®</sup>2.1, which is available from Invitrogen, 1600 Faraday Avenue, Carlsbad, CA 92008, contains an ampicillin resistance gene and may be transformed into E. coli strain DH10B, available from Life Technologies. (See, for instance, Clark, J. M., Nuc. Acids Res. 16:9677-9686 (1988) and Mead, D. et al., Bio/Technology 9: (1991).) Preferably, a polynucleotide of the present invention does not comprise the phage vector sequences identified for the particular clone in Table 5, as well as the corresponding plasmid vector sequences designated above.

The deposited material in the sample assigned the ATCC Deposit Number cited by reference to Table 2 and 5 for any given cDNA clone also may contain one or more additional plasmids, each comprising a cDNA clone different from that given clone. Thus, deposits sharing the same ATCC Deposit Number contain at least a plasmid for each cDNA clone referenced in Table 1.

**TABLE 5**

Libraries owned by Catalog	Catalog Description	Vector	ATCC Deposit
HUKA HUKB HUKC HUKD HUKF HUKG	Human Uterine Cancer	Lambda ZAP II	LP01
HCNA HCNB	Human Colon	Lambda Zap II	LP01
HFFA	Human Fetal Brain, random primed	Lambda Zap II	LP01
HTWA	Resting T-Cell	Lambda ZAP II	LP01
HBQA	Early Stage Human Brain, random primed	Lambda ZAP II	LP01
HLMB HLMF HLMG HLMH HLMI HLMJ HLMM HLMN	breast lymph node CDNA library	Lambda ZAP II	LP01
HCQA HCQB	human colon cancer	Lambda ZAP II	LP01
HMEA HMEC HMED HMEF HMEG HMEI HMEJ HMEK HMEL	Human Microvascular Endothelial Cells, fract. A	Lambda ZAP II	LP01
HUSA HUSC	Human Umbilical Vein Endothelial Cells, fract. A	Lambda ZAP II	LP01
HLQA HLQB	Hepatocellular Tumor	Lambda ZAP II	LP01
HHGA HHGB HHGC HHGD	Hemangiopericytoma	Lambda ZAP II	LP01
HSDM	Human Striatum Depression, re-rescue	Lambda ZAP II	LP01
HUSH	H Umbilical Vein Endothelial Cells, frac A, re-excision	Lambda ZAP II	LP01
HSGS	Salivary gland, subtracted	Lambda ZAP II	LP01
HFXA HFXB HFXC HFXD HFXE HFXF HFXG HFXH	Brain frontal cortex	Lambda ZAP II	LP01
HPQA HPQB HPQC	PERM TF274	Lambda ZAP II	LP01
HFXJ HFXK	Brain Frontal Cortex, re-excision	Lambda ZAP II	LP01
HCWA HCWB HCWC HCWD HCWE HCWF HCWG HCWH HCWI HCWJ HCWK	CD34 positive cells (Cord Blood)	ZAP Express	LP02
HCUA HCUB HCUC	CD34 depleted Buffy Coat (Cord Blood)	ZAP Express	LP02
HRSM	A-14 cell line	ZAP Express	LP02
HRSA	A1-CELL LINE	ZAP Express	LP02
HCUD HCUE HCUF HCUG HCUH HCUI	CD34 depleted Buffy Coat (Cord Blood), re-excision	ZAP Express	LP02
HBXE HBXF HBXG	H. Whole Brain #2, re-excision	ZAP Express	LP02
HRLM	L8 cell line	ZAP Express	LP02
HBXA HBXB HBXC HBXD	Human Whole Brain #2 - Oligo dT > 1.5Kb	ZAP Express	LP02
HUDA HUDB HUDC	Testes	ZAP Express	LP02
HHTM HHTN HHTO	H. hypothalamus, frac A, re-excision	ZAP Express	LP02
HHTL	H. hypothalamus, frac A	ZAP Express	LP02
HASA HASD	Human Adult Spleen	Uni-ZAP XR	LP03
HFKC HFKD HFKE HFKF HFKG	Human Fetal Kidney	Uni-ZAP XR	LP03
HE8A HE8B HE8C HE8D HE8E HE8F HE8M HE8N	Human 8 Week Whole Embryo	Uni-ZAP XR	LP03
HGBA HGBD HGBE HGBF HGBG HGBH HGBI	Human Gall Bladder	Uni-ZAP XR	LP03

Libraries owned by Catalog	Catalog Description	Vector	ATCC Deposit
HLHA HLHB HLHC HLHD HLHE HLHF HLHG HLHH HLHQ	Human Fetal Lung III	Uni-ZAP XR	LP03
HPMA HPMB HPMC HPMD HPME HPMF HPMG HPMH	Human Placenta	Uni-ZAP XR	LP03
HPRA HPRB HPRC HPRD	Human Prostate	Uni-ZAP XR	LP03
HSIA HSIC HSID HSIE	Human Adult Small Intestine	Uni-ZAP XR	LP03
HTEA HTEB HTEC HTEd HTEE HTEF HTEG HTEH HTEI HTEJ HTEK	Human Testes	Uni-ZAP XR	LP03
HTPA HTPB HTPC HTPD HTPe	Human Pancreas Tumor	Uni-ZAP XR	LP03
HTTA HTTB HTTC HTTD HTTE HTTF	Human Testes Tumor	Uni-ZAP XR	LP03
HAPA HAPB HAPC HAPM	Human Adult Pulmonary	Uni-ZAP XR	LP03
HETA HETB HETC HETD HETE HETF HETG HETH HETI	Human Endometrial Tumor	Uni-ZAP XR	LP03
HHFB HHFC HHFD HHFE HHFF HHFG HHFH HHFI	Human Fetal Heart	Uni-ZAP XR	LP03
HHPB HHPc HHPD HHPE HHPF HHPG HHPH	Human Hippocampus	Uni-ZAP XR	LP03
HCE1 HCE2 HCE3 HCE4 HCE5 HCEB HCEC HCEd HCEE HCEF HCEG	Human Cerebellum	Uni-ZAP XR	LP03
HUVB HUVC HUVD HUVE	Human Umbilical Vein, Endo. remake	Uni-ZAP XR	LP03
HSTA HSTB HSTC HSTD	Human Skin Tumor	Uni-ZAP XR	LP03
HTAA HTAB HTAC HTAD HTAE	Human Activated T-Cells	Uni-ZAP XR	LP03
HFEA HFEB HFEC	Human Fetal Epithelium (Skin)	Uni-ZAP XR	LP03
HJPA HJPB HJPC HJPD	HUMAN JURKAT MEMBRANE BOUND POLYSOMES	Uni-ZAP XR	LP03
HESA	Human epithelioid sarcoma	Uni-Zap XR	LP03
HLTA HLTB HLTC HLTD HLTE HLTF	Human T-Cell Lymphoma	Uni-ZAP XR	LP03
HFTA HFTB HFTC HFTD	Human Fetal Dura Mater	Uni-ZAP XR	LP03
HRDA HRDB HRDC HRDD HRDE HRDF	Human Rhabdomyosarcoma	Uni-ZAP XR	LP03
HCAA HCAB HCAC	Cem cells cyclohexamide treated	Uni-ZAP XR	LP03
HRGA HRGB HRGC HRGD	Raji Cells, cyclohexamide treated	Uni-ZAP XR	LP03
HSUA HSUB HSUC HSUM	Supt Cells, cyclohexamide treated	Uni-ZAP XR	LP03
HT4A HT4C HT4D	Activated T-Cells, 12 hrs.	Uni-ZAP XR	LP03
HE9A HE9B HE9C HE9D HE9E HE9F HE9G HE9H HE9M HE9N	Nine Week Old Early Stage Human	Uni-ZAP XR	LP03
HATA HATB HATC HATD HATE	Human Adrenal Gland Tumor	Uni-ZAP XR	LP03
HT5A	Activated T-Cells, 24 hrs.	Uni-ZAP XR	LP03
HFGA HFGM	Human Fetal Brain	Uni-ZAP XR	LP03
HNEA HNEB HNEC HNED HNEE	Human Neutrophil	Uni-ZAP XR	LP03
HBGB HBGD	Human Primary Breast Cancer	Uni-ZAP XR	LP03
HBNA HBNB	Human Normal Breast	Uni-ZAP XR	LP03
HCAS	Cem Cells, cyclohexamide treated, subtra	Uni-ZAP XR	LP03
HHPS	Human Hippocampus, subtracted	pBS	LP03
HKCS HKCU	Human Colon Cancer, subtracted	pBS	LP03
HRGS	Raji cells, cyclohexamide treated,	pBS	LP03

Libraries owned by Catalog	Catalog Description	Vector	ATCC Deposit
	subtracted		
HSUT	Supt cells, cyclohexamide treated, differentially expressed	pBS	LP03
HT4S	Activated T-Cells, 12 hrs. subtracted	Uni-ZAP XR	LP03
HCDA HCDB HCDC HCDD HCDE	Human Chondrosarcoma	Uni-ZAP XR	LP03
HOAA HOAB HOAC	Human Osteosarcoma	Uni-ZAP XR	LP03
HTLA HTLB HTLC HTLD HTLE HTLF	Human adult testis, large inserts	Uni-ZAP XR	LP03
HLMA HLMC HLMD	Breast Lymph node cDNA library	Uni-ZAP XR	LP03
H6EA H6EB H6EC	HL-60, PMA 4H	Uni-ZAP XR	LP03
HTXA HTXB HTXC HTXD HTXE HTXF HTXG HTXH	Activated T-Cell (12hs)/Thiouridine labelledEco	Uni-ZAP XR	LP03
HNFA HNFB HNFC HNFD HNFE HNFF HNFG HNFH HNFJ	Human Neutrophil, Activated	Uni-ZAP XR	LP03
HTOB HTOC	HUMAN TONSILS, FRACTION 2	Uni-ZAP XR	LP03
HMGB	Human OB MG63 control fraction I	Uni-ZAP XR	LP03
HOPB	Human OB HOS control fraction I	Uni-ZAP XR	LP03
HORB	Human OB HOS treated (10 nM E2) fraction I	Uni-ZAP XR	LP03
HSVA HSVB HSVC	Human Chronic Synovitis	Uni-ZAP XR	LP03
HROA	HUMAN STOMACH	Uni-ZAP XR	LP03
HBJA HBJB HBJC HBJD HBJE HBJF HBJG HBJH HBJI HBJJ HBJK	HUMAN B CELL LYMPHOMA	Uni-ZAP XR	LP03
HCRA HCRB HCRC	human corpus colosum	Uni-ZAP XR	LP03
HODA HODB HODC HODD	human ovarian cancer	Uni-ZAP XR	LP03
HDSA	Dermatofibrosarcoma Protuberance	Uni-ZAP XR	LP03
HMWA HMWB HMWC HMWD HMWE HMWF HMWG HMWH HMWI HMWJ	Bone Marrow Cell Line (RS4;11)	Uni-ZAP XR	LP03
HSOA	stomach cancer (human)	Uni-ZAP XR	LP03
HERA	SKIN	Uni-ZAP XR	LP03
HMDA	Brain-medulloblastoma	Uni-ZAP XR	LP03
HGLA HGLB HGLD	Glioblastoma	Uni-ZAP XR	LP03
HEAA	H. Atrophic Endometrium	Uni-ZAP XR	LP03
HBCA HBCB	H. Lymph node breast Cancer	Uni-ZAP XR	LP03
HPWT	Human Prostate BPH, re-excision	Uni-ZAP XR	LP03
HFVG HFVH HFVI	Fetal Liver, subtraction II	pBS	LP03
HNFI	Human Neutrophils, Activated, re-excision	pBS	LP03
HBMB HBMC HBMD	Human Bone Marrow, re-excision	pBS	LP03
HKML HKMM HKMN	H. Kidney Medulla, re-excision	pBS	LP03
HKIX HKIY	H. Kidney Cortex, subtracted	pBS	LP03
HADT	H. Amygdala Depression, subtracted	pBS	LP03
H6AS	HL-60, untreated, subtracted	Uni-ZAP XR	LP03
H6ES	HL-60, PMA 4H, subtracted	Uni-ZAP XR	LP03
H6BS	HL-60, RA 4h, Subtracted	Uni-ZAP XR	LP03
H6CS	HL-60, PMA 1d, subtracted	Uni-ZAP XR	LP03

Libraries owned by Catalog	Catalog Description	Vector	ATCC Deposit
HTXJ HTXK	Activated T-cell(12h)/Thiouridine-re-excision	Uni-ZAP XR	LP03
HMSA HMSB HMSC HMSE HMSF HMSG HMSH HMSI HMSJ HMSK	Monocyte activated	Uni-ZAP XR	LP03
HAGA HAGB HAGC HAGD HAGE HAGF	Human Amygdala	Uni-ZAP XR	LP03
HSRA HSRB HSRE	STROMAL -OSTEOCLASTOMA	Uni-ZAP XR	LP03
HSRD HSRF HSRG HSRH	Human Osteoclastoma Stromal Cells - unamplified	Uni-ZAP XR	LP03
HSQA HSQB HSQC HSQD HSQE HSQF HSQG	Stromal cell TF274	Uni-ZAP XR	LP03
HSKA HSKB HSKC HSKD HSKE HSKF HSKZ	Smooth muscle, serum treated	Uni-ZAP XR	LP03
HSLA HSLB HSLC HSLD HSLE HSLF HSLG	Smooth muscle.control	Uni-ZAP XR	LP03
HSDA HSDD HSDE HSDF HSDG HSDH	Spinal cord	Uni-ZAP XR	LP03
HPWS	Prostate-BPH subtracted II	pBS	LP03
HSKW HSKX HSKY	Smooth Muscle- HASTE normalized	pBS	LP03
HFPB HFPC HFPD	H. Frontal cortex.epileptic;re-excision	Uni-ZAP XR	LP03
HSDI HSDJ HSDK	Spinal Cord, re-excision	Uni-ZAP XR	LP03
HSKN HSKO	Smooth Muscle Serum Treated, Norm	pBS	LP03
HSKG HSKH HSKI	Smooth muscle, serum induced,re-exc	pBS	LP03
HFCA HFCB HFCC HFCD HFCE HFCF	Human Fetal Brain	Uni-ZAP XR	LP04
HPTA HPTB HPTD	Human Pituitary	Uni-ZAP XR	LP04
HTHB HTHC HTHD	Human Thymus	Uni-ZAP XR	LP04
HE6B HE6C HE6D HE6E HE6F HE6G HE6S	Human Whole Six Week Old Embryo	Uni-ZAP XR	LP04
HSSA HSSB HSSC HSSD HSSE HSSF HSSG HSSH HSSI HSSJ HSSK	Human Synovial Sarcoma	Uni-ZAP XR	LP04
HE7T	7 Week Old Early Stage Human, subtracted	Uni-ZAP XR	LP04
HEPA HEPB HEPD	Human Epididymus	Uni-ZAP XR	LP04
HSNA HSNB HSNC HSNM HSNN	Human Synovium	Uni-ZAP XR	LP04
HPFB HPFC HPFD HPFE	Human Prostate Cancer, Stage C fraction	Uni-ZAP XR	LP04
HE2A HE2D HE2E HE2H HE2I HE2M HE2N HE2O	12 Week Old Early Stage Human	Uni-ZAP XR	LP04
HE2B HE2C HE2F HE2G HE2P HE2Q	12 Week Old Early Stage Human, II	Uni-ZAP XR	LP04
HPTS HPTT HPTU	Human Pituitary, subtracted	Uni-ZAP XR	LP04
HAUA HAUB HAUC	Amniotic Cells - TNF induced	Uni-ZAP XR	LP04
HAQA HAQB HAQC HAQD	Amniotic Cells - Primary Culture	Uni-ZAP XR	LP04
HWTB HWTB HWTB	wilm's tumor	Uni-ZAP XR	LP04
HBSD	Bone Cancer, re-excision	Uni-ZAP XR	LP04
HSGB	Salivary gland, re-excision	Uni-ZAP XR	LP04
HSJA HSJB HSJC	Smooth muscle-ILb induced	Uni-ZAP XR	LP04
HSXA HSXB HSXC HSXD	Human Substantia Nigra	Uni-ZAP XR	LP04
HSJA HSJB HSJC	Smooth muscle. IL1b induced	Uni-ZAP XR	LP04

Libraries owned by Catalog	Catalog Description	Vector	ATCC Deposit
HOUA HOUB HOUC HOUD HOUE	Adipocytes	Uni-ZAP XR	LP04
HPWA HPWB HPWC HPWD HPWE	Prostate BPH	Uni-ZAP XR	LP04
HELA HELB HELC HELD HELE HELF HELG HELH	Endothelial cells-control	Uni-ZAP XR	LP04
HEMA HEMB HEMC HEMD HEME HEMF HEMG HEMH	Endothelial-induced	Uni-ZAP XR	LP04
HBIA HBIB HBIC	Human Brain, Striatum	Uni-ZAP XR	LP04
HHSA HHSB HHSC HHSD HHSE	Human Hypothalamus.Schizophrenia	Uni-ZAP XR	LP04
HNGA HNGB HNGC HNGD HNGE HNGF HNGG HNGH HNGI HNGJ	neutrophils control	Uni-ZAP XR	LP04
HNHA HNHB HNHC HNHD HNHE HNHF HNHG HNHG HNHJ HNHJ	Neutrophils IL-1 and LPS induced	Uni-ZAP XR	LP04
HSDB HSDC	STRIATUM DEPRESSION	Uni-ZAP XR	LP04
HHPT	Hypothalamus	Uni-ZAP XR	LP04
HSAT HSAU HSAV HSAW HSAX HSAY HSAZ	Anergic T-cell	Uni-ZAP XR	LP04
HBMS HBMT HBMU HBMV HBMW HBMX	Bone marrow	Uni-ZAP XR	LP04
HOEA HOEB HOEC HOED HOEE HOEF HOEJ	Osteoblasts	Uni-ZAP XR	LP04
HAIA HAIB HAIC HAID HAIE HAIF	Epithelial-TNF $\alpha$ and INF induced	Uni-ZAP XR	LP04
HTGA HTGB HTGC HTGD	Apoptotic T-cell	Uni-ZAP XR	LP04
HMCA HMCB HMCC HMCD HMCE	Macrophage-oxLDL	Uni-ZAP XR	LP04
HMAA HMAB HMAE HMAF HMAE HMAF HMAG	Macrophage (GM-CSF treated)	Uni-ZAP XR	LP04
HPHA	Normal Prostate	Uni-ZAP XR	LP04
HP1A HP1B HP1C	LNCAP prostate cell line	Uni-ZAP XR	LP04
HPJA HPJB HPJC	PC3 Prostate cell line	Uni-ZAP XR	LP04
HOSE HOSF HOSG	Human Osteoclastoma, re-excision	Uni-ZAP XR	LP04
HTGE HTGF	Apoptotic T-cell, re-excision	Uni-ZAP XR	LP04
HMAJ HMAK	H Macrophage (GM-CSF treated), re-excision	Uni-ZAP XR	LP04
HACB HACC HACD	Human Adipose Tissue, re-excision	Uni-ZAP XR	LP04
HFPA	H. Frontal Cortex, Epileptic	Uni-ZAP XR	LP04
HFAA HFAB HFAC HFAD HFAE	Alzheimers, spongy change	Uni-ZAP XR	LP04
HFAM	Frontal Lobe, Dementia	Uni-ZAP XR	LP04
HMIA HMIB HMIC	Human Manic Depression Tissue	Uni-ZAP XR	LP04
HTSA HTSE HTSF HTSG HTSH	Human Thymus	pBS	LP05
HPBA HPBB HPBC HPBD HPBE	Human Pineal Gland	pBS	LP05
HSAA HSAB HSAC	HSA 172 Cells	pBS	LP05
HSBA HSBB HSBC HSBM	HSC172 cells	pBS	LP05
HJAA HJAB HJAC HJAD	Jurkat T-cell G1 phase	pBS	LP05
HJBA HJBB HJBC HJBD	Jurkat T-Cell, S phase	pBS	LP05
HAFA HAFB	Aorta endothelial cells + TNF- $\alpha$	pBS	LP05
HAWA HAWB HAWC	Human White Adipose	pBS	LP05
HTNA HTNB	Human Thyroid	pBS	LP05
HONA	Normal Ovary, Premenopausal	pBS	LP05

Libraries owned by Catalog	Catalog Description	Vector	ATCC Deposit
HARA HARB	Human Adult Retina	pBS	LP05
HLJA HLJB	Human Lung	pCMVSPORT 1	LP06
HOFM HOFN HOFO	H. Ovarian Tumor, II, OV5232	pCMVSPORT 2.0	LP07
HOGA HOGB HOGC	OV 10-3-95	pCMVSPORT 2.0	LP07
HCGL	CD34+cells. II	pCMVSPORT 2.0	LP07
HDLA	Hodgkin's Lymphoma I	pCMVSPORT 2.0	LP07
HDTA HDTB HDTC HDTD HDTE	Hodgkin's Lymphoma II	pCMVSPORT 2.0	LP07
HKAA HKAB HKAC HKAD HKAE HKAF HKAG HKAH	Keratinocyte	pCMVSPORT2.0	LP07
HCIM	CAPFINDER, Crohn's Disease, lib 2	pCMVSPORT 2.0	LP07
HKAL	Keratinocyte, lib 2	pCMVSPORT2.0	LP07
HKAT	Keratinocyte, lib 3	pCMVSPORT2.0	LP07
HNDA	Nasal polyps	pCMVSPORT2.0	LP07
HDRA	H. Primary Dendritic Cells.lib 3	pCMVSPORT2.0	LP07
HOHA HOHB HOHC	Human Osteoblasts II	pCMVSPORT2.0	LP07
HLDA HLDB HLDC	Liver, Hepatoma	pCMVSPORT3.0	LP08
HLDN HLDO HLDP	Human Liver, normal	pCMVSPORT3.0	LP08
HMTA	pBMC stimulated w/ poly I/C	pCMVSPORT3.0	LP08
HNTA	NTERA2, control	pCMVSPORT3.0	LP08
HDPA HDPB HDPC HDPD HDPF HDPG HDPH HDPI HDPJ HDPK	Primary Dendritic Cells, lib 1	pCMVSPORT3.0	LP08
HDPM HDPN HDPO HDPP	Primary Dendritic cells, frac 2	pCMVSPORT3.0	LP08
HMUA HMUB HMUC	Myeloid Progenitor Cell Line	pCMVSPORT3.0	LP08
HHEA HHEB HHEC HHED	T Cell helper I	pCMVSPORT3.0	LP08
HHEM HHEN HHEO HHEP	T cell helper II	pCMVSPORT3.0	LP08
HEQA HEQB HEQC	Human endometrial stromal cells	pCMVSPORT3.0	LP08
HJMA HJMB	Human endometrial stromal cells- treated with progesterone	pCMVSPORT3.0	LP08
HSWA HSWB HSWC	Human endometrial stromal cells- treated with estradiol	pCMVSPORT3.0	LP08
HSYA HSYB HSYC	Human Thymus Stromal Cells	pCMVSPORT3.0	LP08
HLWA HLWB HLWC	Human Placenta	pCMVSPORT3.0	LP08
HRAA HRAB HRAC	Rejected Kidney, lib 4	pCMVSPORT3.0	LP08
HMTM	PCR, pBMC I/C treated	PCRII	LP09
HMJA	H. Meningioma, M6	pSport 1	LP10
HMKA HMKB HMKE HMKE	H. Meningioma, M1	pSport 1	LP10
HUSG HUSI	Human umbilical vein endothelial cells, IL-4 induced	pSport 1	LP10
HUSX HUSY	Human Umbilical Vein Endothelial Cells, uninduced	pSport 1	LP10
HOFA	Ovarian Tumor I, OV5232	pSport 1	LP10
HCFA HCFB HCFC HCFC	T-Cell PHA 16 hrs	pSport 1	LP10
HCFL HCFM HCFN HCFO	T-Cell PHA 24 hrs	pSport 1	LP10
HADA HADC HADD HADE HADF HADG	Human Adipose	pSport 1	LP10
HOVA HOVB HOVC	Human Ovary	pSport 1	LP10



Libraries owned by Catalog	Catalog Description	Vector	ATCC Deposit
HTWB HTWC HTWD HTWE HTWF	Resting T-Cell Library, II	pSport 1	LP10
HMMA	Spleen metastatic melanoma	pSport 1	LP10
HLYA HLYB HLYC HLYD HLYE	Spleen, Chronic lymphocytic leukemia	pSport 1	LP10
HCGA	CD34+ cell. I	pSport 1	LP10
HEOM HEON	Human Eosinophils	pSport 1	LP10
HTDA	Human Tonsil, Lib 3	pSport 1	LP10
HSPA	Salivary Gland, Lib 2	pSport 1	LP10
HCHA HCHB HCHC	Breast Cancer cell line, MDA 36	pSport 1	LP10
HCHM HCHN	Breast Cancer Cell line, angiogenic	pSport 1	LP10
HCIA	Crohn's Disease	pSport 1	LP10
HDAA HDAB HDAC	HEL cell line	pSport 1	LP10
HABA	Human Astrocyte	pSport 1	LP10
HUFA HUFB HUFC	Ulcerative Colitis	pSport 1	LP10
HNTM	NTERA2 + retinoic acid, 14 days	pSport 1	LP10
HDQA	Primary Dendritic cells, CapFinder2, frac 1	pSport 1	LP10
HDQM	Primary Dendritic Cells, CapFinder, frac 2	pSport 1	LP10
HLDX	Human Liver, normal, CapFinder	pSport 1	LP10
HULA HULB HULC	Human Dermal Endothelial Cells, untreated	pSport 1	LP10
HUMA	Human Dermal Endothelial cells, treated	pSport 1	LP10
HCJA	Human Stromal Endometrial fibroblasts, untreated	pSport 1	LP10
HCJM	Human Stromal endometrial fibroblasts, treated w/ estradiol	pSport 1	LP10
HEDA	Human Stromal endometrial fibroblasts, treated with progesterone	pSport 1	LP10
HFNA	Human ovary tumor cell OV350721	pSport 1	LP10
HKGA HKGB HKGC HKGD	Merkel Cells	pSport 1	LP10
HISA HISB HISC	Pancreas Islet Cell Tumor	pSport 1	LP10
HLSA	Skin, burned	pSport 1	LP10
HBZA	Prostate, BPH, Lib 2	pSport 1	LP10
HBZS	Prostate BPH, Lib 2, subtracted	pSport 1	LP10
HFIA HFIB HFIC	Synovial Fibroblasts (control)	pSport 1	LP10
HFIH HFII HFIJ	Synovial hypoxia	pSport 1	LP10
HFIT HFIU HFIV	Synovial IL-1/TNF stimulated	pSport 1	LP10
HGCA	Mesangial cell, frac 1	pSport 1	LP10
HMVA HMVB HMVC	Bone Marrow Stromal Cell, untreated	pSport 1	LP10
HFIX HFIY HFIZ	Synovial Fibroblasts (II1/TNF), sub	pSport 1	LP10
HFOX HFOY HFOZ	Synovial hypoxia-RSF subtracted	pSport 1	LP10
HMQA HMQB HMQC HMQD	Human Activated Monocytes	Uni-ZAP XR	LP11
HLIA HLIB HLIC	Human Liver	pCMVSPORT 1	LP012
HHBA HHBB HHBC HHBD HHBE	Human Heart	pCMVSPORT 1	LP012
HBBA HBBB	Human Brain	pCMVSPORT 1	LP012
HLJA HLJB HLJC HLJD HLJE	Human Lung	pCMVSPORT 1	LP012

Libraries owned by Catalog	Catalog Description	Vector	ATCC Deposit
HOGA HOGB HOGC	Ovarian Tumor	pCMVSPORT 2.0	LP012
HTJM	Human Tonsils, Lib 2	pCMVSPORT 2.0	LP012
HAMF HAMG	KMH2	pCMVSPORT 3.0	LP012
HAJA HAJB HAJC	L428	pCMVSPORT 3.0	LP012
HWBA HWBB HWBC HWBD HWBE	Dendritic cells, pooled	pCMVSPORT 3.0	LP012
HWAA HWAB HWAC HWAD HWAE	Human Bone Marrow, treated	pCMVSPORT 3.0	LP012
HYAA HYAB HYAC	B Cell lymphoma	pCMVSPORT 3.0	LP012
HWHG HWHH HWHI	Healing groin wound, 6.5 hours post incision	pCMVSPORT 3.0	LP012
HWHP HWHQ HWHR	Healing groin wound, 7.5 hours post incision	pCMVSPORT 3.0	LP012
HARM	Healing groin wound - zero hr post-incision (control)	pCMVSPORT 3.0	LP012
HBIM	Olfactory epithelium: nasalcavity	pCMVSPORT 3.0	LP012
HWDA	Healing Abdomen wound; 70&90 min post incision	pCMVSPORT 3.0	LP012
HWEA	Healing Abdomen Wound;15 days post incision	pCMVSPORT 3.0	LP012
HWJA	Healing Abdomen Wound;21&29 days	pCMVSPORT 3.0	LP012
HNAL	Human Tongue, frac 2	pSport1	LP012
HMJA	H. Meningima, M6	pSport1	LP012
HMKA HMKB HMKC HMKD HMKE	H. Meningima, M1	pSport1	LP012
HOFA	Ovarian Tumor I, OV5232	pSport1	LP012
HCFA HCFB HCFC HCFD	T-Cell PHA 16 hrs	pSport1	LP012
HCFL HCFM HCFN HCFO	T-Cell PHA 24 hrs	pSport1	LP012
HMMA HMMB HMMC	Spleen metastatic melanoma	pSport1	LP012
HTDA	Human Tonsil, Lib 3	pSport1	LP012
HDBA	Human Fetal Thymus	pSport1	LP012
HDAU	Pericardium	pSport1	LP012
HBZA	Prostate.BPH, Lib 2	pSport1	LP012
HWCA	Larynx tumor	pSport1	LP012
HWKA	Normal lung	pSport1	LP012
HSMB	Bone marrow stroma,treated	pSport1	LP012
HBHM	Normal trachea	pSport1	LP012
HLFC	Human Larynx	pSport1	LP012
HLRB	Siebben Polyposis	pSport1	LP012
HNIA	Mammary Gland	pSport1	LP012
HNJB	Palate carcinoma	pSport1	LP012
HNKA	Palate normal	pSport1	LP012
HMZA	Pharynx carcinoma	pSport1	LP012
HABG	Cheek Carcinoma	pSport1	LP012
HMZM	Pharynx Carcinoma	pSport1	LP012
HDRM	Larynx Carcinoma	pSport1	LP012
HVAA	Pancreas normal PCA4 No	pSport1	LP012
HICA	Tongue carcinoma	pSport1	LP012
HUKA HUKB HUKC HUKD HUKF	Human Uterine Cancer	Lambda ZAP II	LP013
HFFA	Human Fetal Brain, random primed	Lambda ZAP II	LP013
HTUA	Activated T-cell labeled with 4-thioluri	Lambda ZAP II	LP013

Libraries owned by Catalog	Catalog Description	Vector	ATCC Deposit
HBQA	Early Stage Human Brain. random primed	Lambda ZAP II	LP013
HMEB	Human microvascular Endothelial cells, fract. B	Lambda ZAP II	LP013
HUSH	Human Umbilical Vein Endothelial cells, fract. A, re-excision	Lambda ZAP II	LP013
HLQC HLQD	Hepatocellular tumor. re-excision	Lambda ZAP II	LP013
HTWJ HTWK HTWL	Resting T-cell, re-excision	Lambda ZAP II	LP013
HF6S	Human Whole 6 week Old Embryo (II), subt	pBluescript	LP013
HHPS	Human Hippocampus, subtracted	pBluescript	LP013
HLIS	LNCAp. differential expression	pBluescript	LP013
HLHS HLHT	Early Stage Human Lung, Subtracted	pBluescript	LP013
HSUS	Supt cells, cyclohexamide treated, subtracted	pBluescript	LP013
HSUT	Supt cells, cyclohexamide treated, differentially expressed	pBluescript	LP013
HSDS	H. Striatum Depression, subtracted	pBluescript	LP013
HPTZ	Human Pituitary, Subtracted VII	pBluescript	LP013
HSDX	H. Striatum Depression, subt II	pBluescript	LP013
HSDZ	H. Striatum Depression, subt	pBluescript	LP013
HPBA HPBB HPBC HPBD HPBE	Human Pineal Gland	pBluescript SK-	LP013
HRTA	Colorectal Tumor	pBluescript SK-	LP013
HSBA HSBB HSBC HSBM	HSC172 cells	pBluescript SK-	LP013
HJAA HJAB HJAC HJAD	Jurkat T-cell G1 phase	pBluescript SK-	LP013
HJBA HJBB HJBC HJBD	Jurkat T-cell, S1 phase	pBluescript SK-	LP013
HTNA HTNB	Human Thyroid	pBluescript SK-	LP013
HAHA HAHB	Human Adult Heart	Uni-ZAP XR	LP013
HE6A	Whole 6 week Old Embryo	Uni-ZAP XR	LP013
HFCA HFCE HFCD HFCE	Human Fetal Brain	Uni-ZAP XR	LP013
HFKE HFKE HFKE HFKE HFKE	Human Fetal Kidney	Uni-ZAP XR	LP013
HGBA HGBD HGBE HGBF HGBG	Human Gall Bladder	Uni-ZAP XR	LP013
HPRA HPRB HPRC HPRD	Human Prostate	Uni-ZAP XR	LP013
HTEA HTEB HTEC HTED HTEE	Human Testes	Uni-ZAP XR	LP013
HTTA HTTB HTTC HTTD HTTE	Human Testes Tumor	Uni-ZAP XR	LP013
HYBA HYBB	Human Fetal Bone	Uni-ZAP XR	LP013
HFLA	Human Fetal Liver	Uni-ZAP XR	LP013
HHFB HHFC HHFD HHFE HHFF	Human Fetal Heart	Uni-ZAP XR	LP013
HUVB HUVB HUVB HUVB	Human Umbilical Vein, End. remake	Uni-ZAP XR	LP013
HTHB HTHC HTHD	Human Thymus	Uni-ZAP XR	LP013
HSTA HSTB HSTC HSTD	Human Skin Tumor	Uni-ZAP XR	LP013
HTAA HTAB HTAC HTAD HTAE	Human Activated T-cells	Uni-ZAP XR	LP013
HFEA HFEB HFEC	Human Fetal Epithelium (skin)	Uni-ZAP XR	LP013
HJPA HJPB HJPC HJPD	Human Jurkat Membrane Bound Polysomes	Uni-ZAP XR	LP013
HESA	Human Epithelioid Sarcoma	Uni-ZAP XR	LP013
HALS	Human Adult Liver, Subtracted	Uni-ZAP XR	LP013
HFTA HFTB HFTC HFTD	Human Fetal Dura Mater	Uni-ZAP XR	LP013
HCAA HCAB HCAC	Cem cells, cyclohexamide treated	Uni-ZAP XR	LP013

Libraries owned by Catalog	Catalog Description	Vector	ATCC Deposit
HRGA HRGB HRGC HRGD	Raji Cells. cyclohexamide treated	Uni-ZAP XR	LP013
HE9A HE9B HE9C HE9D HE9E	Nine Week Old Early Stage Human	Uni-ZAP XR	LP013
HSFA	Human Fibrosarcoma	Uni-ZAP XR	LP013
HATA HATB HATC HATD HATE	Human Adrenal Gland Tumor	Uni-ZAP XR	LP013
HTRA	Human Trachea Tumor	Uni-ZAP XR	LP013
HE2A HE2D HE2E HE2H HE2I	12 Week Old Early Stage Human	Uni-ZAP XR	LP013
HE2B HE2C HE2F HE2G HE2P	12 Week Old Early Stage Human. II	Uni-ZAP XR	LP013
HNEA HNEB HNEC HNED HNEE	Human Neutrophil	Uni-ZAP XR	LP013
HBGA	Human Primary Breast Cancer	Uni-ZAP XR	LP013
HPTS HPTT HPTU	Human Pituitary, subtracted	Uni-ZAP XR	LP013
HMQA HMQB HMQC HMQD	Human Activated Monocytes	Uni-ZAP XR	LP013
HOAA HOAB HOAC	Human Osteosarcoma	Uni-ZAP XR	LP013
HTOA HTOD HTOE HTOF HTOG	human tonsils	Uni-ZAP XR	LP013
HMGB	Human OB MG63 control fraction I	Uni-ZAP XR	LP013
HOPB	Human OB HOS control fraction I	Uni-ZAP XR	LP013
HOQB	Human OB HOS treated (1 nM E2) fraction I	Uni-ZAP XR	LP013
HAUA HAUB HAUC	Amniotic Cells - TNF induced	Uni-ZAP XR	LP013
HAQA HAQB HAQC HAQD	Amniotic Cells - Primary Culture	Uni-ZAP XR	LP013
HROA HROC	HUMAN STOMACH	Uni-ZAP XR	LP013
HBJA HBJB HBJC HBJD HBJE	HUMAN B CELL LYMPHOMA	Uni-ZAP XR	LP013
HODA HODB HODC HODD	human ovarian cancer	Uni-ZAP XR	LP013
HCPA	Corpus Callosum	Uni-ZAP XR	LP013
HSOA	stomach cancer (human)	Uni-ZAP XR	LP013
HERA	SKIN	Uni-ZAP XR	LP013
HMDA	Brain-medulloblastoma	Uni-ZAP XR	LP013
HGLA HGLB HGLD	Glioblastoma	Uni-ZAP XR	LP013
HWTA HWTB HWTC	wilm's tumor	Uni-ZAP XR	LP013
HEAA	H. Atrophic Endometrium	Uni-ZAP XR	LP013
HAPN HAPO HAPR HAPQ HAPR	Human Adult Pulmonary;re-excision	Uni-ZAP XR	LP013
HLTG HLTH	Human T-cell lymphoma;re-excision	Uni-ZAP XR	LP013
HAHC HAHD HAHE	Human Adult Heart;re-excision	Uni-ZAP XR	LP013
HAGA HAGB HAGC HAGD HAGE	Human Amygdala	Uni-ZAP XR	LP013
HSJA HSJB HSJC	Smooth muscle-ILb induced	Uni-ZAP XR	LP013
HSJA HSJB HSJC	Smooth muscle, IL1b induced	Uni-ZAP XR	LP013
HPWA HPWB HPWC HPWD HPWE	Prostate BPH	Uni-ZAP XR	LP013
HPJA HPJB HPJC	LNCAP prostate cell line	Uni-ZAP XR	LP013
HPJA HPJB HPJC	PC3 Prostate cell line	Uni-ZAP XR	LP013
HBTA	Bone Marrow Stroma, TNF&LPS ind	Uni-ZAP XR	LP013
HMCF HMCB HMCH HMCJ HMCJ	Macrophage-oxLDL; re-excision	Uni-ZAP XR	LP013
HAGG HAGH HAGI	Human Amygdala;re-excision	Uni-ZAP XR	LP013
HACA	H. Adipose Tissue	Uni-ZAP XR	LP013
HKFB	K562 + PMA (36 hrs);re-excision	ZAP Express	LP013
HCWT HCWU HCWV	CD34 positive cells (cord blood);re-ex	ZAP Express	LP013
HBWA	Whole brain	ZAP Express	LP013
HBXA HBXB HBXC HBXD	Human Whole Brain #2 - Oligo dT > 1.5Kb	ZAP Express	LP013

Libraries owned by Catalog	Catalog Description	Vector	ATCC Deposit
HAVM	Temporal cortex-Alzheimer	pT-Adv	LP014
HAVT	Hippocampus, Alzheimer Subtracted	pT-Adv	LP014
HHAS	CHME Cell Line	Uni-ZAP XR	LP014
HAJR	Larynx normal	pSport 1	LP014
HWLE HWLF HWLG HWLH	Colon Normal	pSport 1	LP014
HCRM HCRN HCRO	Colon Carcinoma	pSport 1	LP014
HWLI HWLJ HWLK	Colon Normal	pSport 1	LP014
HWLH HWLR HWLS HWLT	Colon Tumor	pSport 1	LP014
HBFM	Gastrocnemius Muscle	pSport 1	LP014
HBOD HBOE	Quadriceps Muscle	pSport 1	LP014
HBKD HBKE	Soleus Muscle	pSport 1	LP014
HCCM	Pancreatic Langerhans	pSport 1	LP014
HWGA	Larynx carcinoma	pSport 1	LP014
HWGM HWGN	Larynx carcinoma	pSport 1	LP014
HWLA HWLB HWLC	Normal colon	pSport 1	LP014
HWLM HWLN	Colon Tumor	pSport 1	LP014
HVAM HVAN HVAO	Pancreas Tumor	pSport 1	LP014
HWGQ	Larynx carcinoma	pSport 1	LP014
HAQM HAQN	Salivary Gland	pSport 1	LP014
HASM	Stomach; normal	pSport 1	LP014
HBCM	Uterus; normal	pSport 1	LP014
HCDM	Testis; normal	pSport 1	LP014
HDJM	Brain; normal	pSport 1	LP014
HEFM	Adrenal Gland; normal	pSport 1	LP014
HBAA	Rectum normal	pSport 1	LP014
HFDH	Rectum tumour	pSport 1	LP014
HGAM	Colon, normal	pSport 1	LP014
HHMM	Colon, tumour	pSport 1	LP014
HCLB HCLC	Human Lung Cancer	Lambda Zap II	LP015
HRLA	L1 Cell line	ZAP Express	LP015
HHAM	Hypothalamus, Alzheimer's	pCMVSPORT 3.0	LP015
HKBA	Ku 812F Basophils Line	pSport 1	LP015
HS2S	Saos2, Dexamethasone Treated	pSport 1	LP016
HA5A	Lung Carcinoma A549 TNFalpha activated	pSport 1	LP016
HTFM	TF-1 Cell Line GM-CSF Treated	pSport 1	LP016
HYAS	Thyroid Tumour	pSport 1	LP016
HUTS	Larynx Normal	pSport 1	LP016
HXOA	Larynx Tumor	pSport 1	LP016
HEAH	Ea.hy.926 cell line	pSport 1	LP016
HINA	Adenocarcinoma Human	pSport 1	LP016
HRMA	Lung Mesothelium	pSport 1	LP016
HLCL	Human Pre-Differentiated Adipocytes	Uni-Zap XR	LP017
HS2A	Saos2 Cells	pSport 1	LP020
HS2I	Saos2 Cells; Vitamin D3 Treated	pSport 1	LP020
HUCM	CHME Cell Line, untreated	pSport 1	LP020
HEPN	Aryepiglottis Normal	pSport 1	LP020

Libraries owned by Catalog	Catalog Description	Vector	ATCC Deposit
HPSN	Sinus Piniformis Tumour	pSport 1	LP020
HNSA	Stomach Normal	pSport 1	LP020
HNSM	Stomach Tumour	pSport 1	LP020
HNLA	Liver Normal Met5No	pSport 1	LP020
HUTA	Liver Tumour Met 5 Tu	pSport 1	LP020
HOCN	Colon Normal	pSport 1	LP020
HOCT	Colon Tumor	pSport 1	LP020
HTNT	Tongue Tumour	pSport 1	LP020
HLXN	Larynx Normal	pSport 1	LP020
HLXT	Larynx Tumour	pSport 1	LP020
HTYN	Thymus	pSport 1	LP020
HPLN	Placenta	pSport 1	LP020
HTNG	Tongue Normal	pSport 1	LP020
HZAA	Thyroid Normal (SDCA2 No)	pSport 1	LP020
HWES	Thyroid Thyroiditis	pSport 1	LP020
HFHD	Ficolled Human Stromal Cells, 5Fu treated	pTrip1Ex2	LP021
HFHM,HFHN	Ficolled Human Stromal Cells, Untreated	pTrip1Ex2	LP021
HPCI	Hep G2 Cells, lambda library	lambda Zap-CMV XR	LP021
HBCA,HBCB,HBCC	H. Lymph node breast Cancer	Uni-ZAP XR	LP021
HCOK	Chondrocytes	pSPORT1	LP022
HDCA, HDCB, HDCC	Dendritic Cells From CD34 Cells	pSPORT1	LP022
HDMA, HDMB	CD40 activated monocyte dendritic cells	pSPORT1	LP022
HDDM, HDDN, HDDO	LPS activated derived dendritic cells	pSPORT1	LP022
HPCR	Hep G2 Cells, PCR library	lambda Zap-CMV XR	LP022
HAAA, HAAB, HAAC	Lung, Cancer (4005313A3): Invasive Poorly Differentiated Lung Adenocarcinoma	pSPORT1	LP022
HIPA, HIPB, HIPC	Lung, Cancer (4005163 B7): Invasive, Poorly Diff. Adenocarcinoma, Metastatic	pSPORT1	LP022
HOOH, HOOI	Ovary, Cancer: (4004562 B6) Papillary Serous Cystic Neoplasm, Low Malignant Pot	pSPORT1	LP022
HIDA	Lung, Normal: (4005313 B1)	pSPORT1	LP022
HUJA,HUJB,HUJC,HUJD,HUJE	B-Cells	pCMVSPORT 3.0	LP022
HNOA,HNOB,HNOC,HNOD	Ovary, Normal: (9805C040R)	pSPORT1	LP022
HNLN	Lung, Normal: (4005313 B1)	pSPORT1	LP022
HSCL	Stromal Cells	pSPORT1	LP022
HAAX	Lung, Cancer: (4005313 A3) Invasive Poorly-differentiated Metastatic lung adenocarcinoma	pSPORT1	LP022
HUUA,HUUB,HUUC,HUUD	B-cells (unstimulated)	pTrip1Ex2	LP022
HWWA,HWWB,HWWC,HWWD,HWE,HWWF,HWWG	B-cells (stimulated)	pSPORT1	LP022
HCCC	Colon, Cancer: (9808C064R)	pCMVSPORT 3.0	LP023
HPDO HPDP HPDQ HPDR HPD	Ovary, Cancer (9809C332): Poorly differentiated adenocarcinoma	pSport 1	LP023

Libraries owned by Catalog	Catalog Description	Vector	ATCC Deposit
HPCO HPCP HPCQ HPCT	Ovary, Cancer (15395A1F): Grade II Papillary Carcinoma	pSport 1	LP023
HOCM HOCO HOCQ HOCQ	Ovary, Cancer: (15799A1F) Poorly differentiated carcinoma	pSport 1	LP023
HCBM HCBN HCBO	Breast, Cancer: (4004943 A5)	pSport 1	LP023
HNBT HNBU HNBV	Breast, Normal: (4005522B2)	pSport 1	LP023
HBCP HBCQ	Breast, Cancer: (4005522 A2)	pSport 1	LP023
HBCJ	Breast, Cancer: (9806C012R)	pSport 1	LP023
HSAM HSAN	Stromal cells 3.88	pSport 1	LP023
HVCA HVCB HVCC HVCD	Ovary, Cancer: (4004332 A2)	pSport 1	LP023
HSCK HSEN HSEO	Stromal cells (HBM3.18)	pSport 1	LP023
HSCP HSCQ	stromal cell clone 2.5	pSport 1	LP023
HUXA	Breast Cancer: (4005385 A2)	pSport 1	LP023
HCOM HCON HCOO HCOP HCOQ	Ovary, Cancer (4004650 A3): Well-Differentiated Micropapillary Serous Carcinoma	pSport 1	LP023
HBNM	Breast, Cancer: (9802C020E)	pSport 1	LP023
HVVA HVVB HVVC HVVD HVVE	Human Bone Marrow, treated	pSport 1	LP023

Two approaches can be used to isolate a particular clone from the deposited sample of plasmid DNAs cited for that clone in Table 5. First, a plasmid is directly isolated by screening the clones using a polynucleotide probe corresponding to the nucleotide sequence of SEQ ID NO:X.

5        Particularly, a specific polynucleotide with 30-40 nucleotides is synthesized using an Applied Biosystems DNA synthesizer according to the sequence reported. The oligonucleotide is labeled, for instance, with  $^{32}\text{P}$ - $\gamma$ -ATP using T4 polynucleotide kinase and purified according to routine methods. (E.g., Maniatis et al., *Molecular Cloning: A Laboratory Manual*, Cold Spring Harbor Press, Cold Spring, NY (1982).) The plasmid  
10        mixture is transformed into a suitable host, as indicated above (such as XL-1 Blue (Stratagene)) using techniques known to those of skill in the art, such as those provided by the vector supplier or in related publications or patents cited above. The transformants are plated on 1.5% agar plates (containing the appropriate selection agent, e.g., ampicillin) to a density of about 150 transformants (colonies) per plate. These plates are screened using  
15        Nylon membranes according to routine methods for bacterial colony screening (e.g., Sambrook et al., *Molecular Cloning: A Laboratory Manual*, 2nd Edit., (1989), Cold Spring Harbor Laboratory Press, pages 1.93 to 1.104), or other techniques known to those of skill in the art.

          Alternatively, two primers of 17-20 nucleotides derived from both ends of the  
20        nucleotide sequence of SEQ ID NO:X are synthesized and used to amplify the desired cDNA using the deposited cDNA plasmid as a template. The polymerase chain reaction is carried out under routine conditions, for instance, in 25  $\mu\text{l}$  of reaction mixture with 0.5  $\mu\text{g}$  of the above cDNA template. A convenient reaction mixture is 1.5-5 mM  $\text{MgCl}_2$ , 0.01% (w/v) gelatin, 20  $\mu\text{M}$  each of dATP, dCTP, dGTP, dTTP, 25 pmol of each primer and 0.25 Unit of  
25        Taq polymerase. Thirty five cycles of PCR (denaturation at 94°C for 1 min; annealing at 55°C for 1 min; elongation at 72°C for 1 min) are performed with a Perkin-Elmer Cetus automated thermal cycler. The amplified product is analyzed by agarose gel electrophoresis and the DNA band with expected molecular weight is excised and purified. The PCR  
30        product is verified to be the selected sequence by subcloning and sequencing the DNA product.

          Several methods are available for the identification of the 5' or 3' non-coding portions of a gene which may not be present in the deposited clone. These methods include but are not



limited to, filter probing, clone enrichment using specific probes, and protocols similar or identical to 5' and 3' "RACE" protocols which are well known in the art. For instance, a method similar to 5' RACE is available for generating the missing 5' end of a desired full-length transcript. (Fromont-Racine et al., Nucleic Acids Res. 21(7):1683-1684 (1993).)

5 Briefly, a specific RNA oligonucleotide is ligated to the 5' ends of a population of RNA presumably containing full-length gene RNA transcripts. A primer set containing a primer specific to the ligated RNA oligonucleotide and a primer specific to a known sequence of the gene of interest is used to PCR amplify the 5' portion of the desired full-length gene. This amplified product may then be sequenced and used to generate the full  
10 length gene.

This above method starts with total RNA isolated from the desired source, although poly-A<sup>+</sup> RNA can be used. The RNA preparation can then be treated with phosphatase if necessary to eliminate 5' phosphate groups on degraded or damaged RNA which may interfere with the later RNA ligase step. The phosphatase should then be inactivated and the  
15 RNA treated with tobacco acid pyrophosphatase in order to remove the cap structure present at the 5' ends of messenger RNAs. This reaction leaves a 5' phosphate group at the 5' end of the cap cleaved RNA which can then be ligated to an RNA oligonucleotide using T4 RNA ligase.

This modified RNA preparation is used as a template for first strand cDNA synthesis  
20 using a gene specific oligonucleotide. The first strand synthesis reaction is used as a template for PCR amplification of the desired 5' end using a primer specific to the ligated RNA oligonucleotide and a primer specific to the known sequence of the gene of interest. The resultant product is then sequenced and analyzed to confirm that the 5' end sequence belongs to the desired gene.

25

***Example 2: Isolation of Genomic Clones Corresponding to a Polynucleotide***

A human genomic PI library (Genomic Systems, Inc.) is screened by PCR using primers selected for the sequence corresponding to SEQ ID NO:X, according to the method  
30 described in Example 1. (See also, Sambrook.)

***Example 3: Tissue specific expression analysis***

The Human Genome Sciences, Inc. (HGS) database is derived from sequencing tissue specific cDNA libraries. Libraries generated from a particular tissue are selected and the specific tissue expression pattern of EST groups or assembled contigs within these libraries is determined by comparison of the expression patterns of those groups or contigs within the entire database. ESTs which show tissue specific expression are selected.

The original clone from which the specific EST sequence was generated, is obtained from the catalogued library of clones and the insert amplified by PCR using methods known in the art. The PCR product is denatured then transferred in 96 well format to a nylon membrane (Schleicher and Scheull) generating an array filter of tissue specific clones. Housekeeping genes, maize genes, and known tissue specific genes are included on the filters. These targets can be used in signal normalization and to validate assay sensitivity. Additional targets are included to monitor probe length and specificity of hybridization.

Radioactively labeled hybridization probes are generated by first strand cDNA synthesis per the manufacturer's instructions (Life Technologies) from mRNA/RNA samples prepared from the specific tissue being analyzed. The hybridization probes are purified by gel exclusion chromatography, quantitated, and hybridized with the array filters in hybridization bottles at 65°C overnight. The filters are washed under stringent conditions and signals are captured using a Fuji phosphorimager.

Data is extracted using AIS software and following background subtraction, signal normalization is performed. This includes a normalization of filter-wide expression levels between different experimental runs. Genes that are differentially expressed in the tissue of interest are identified and the full length sequence of these clones is generated.

***Example 4: Chromosomal Mapping of the Polynucleotides***

An oligonucleotide primer set is designed according to the sequence at the 5' end of SEQ ID NO:X. This primer preferably spans about 100 nucleotides. This primer set is then used in a polymerase chain reaction under the following set of conditions : 30 seconds, 95°C; 1 minute, 56°C; 1 minute, 70°C. This cycle is repeated 32 times followed by one 5 minute

cycle at 70°C. Human, mouse, and hamster DNA is used as template in addition to a somatic cell hybrid panel containing individual chromosomes or chromosome fragments (Bios, Inc). The reactions is analyzed on either 8% polyacrylamide gels or 3.5 % agarose gels. Chromosome mapping is determined by the presence of an approximately 100 bp PCR  
5 fragment in the particular somatic cell hybrid.

***Example 5: Bacterial Expression of a Polypeptide***

A polynucleotide encoding a polypeptide of the present invention is amplified using  
10 PCR oligonucleotide primers corresponding to the 5' and 3' ends of the DNA sequence, as outlined in Example 1, to synthesize insertion fragments. The primers used to amplify the cDNA insert should preferably contain restriction sites, such as BamHI and XbaI, at the 5' end of the primers in order to clone the amplified product into the expression vector. For example, BamHI and XbaI correspond to the restriction enzyme sites on the bacterial  
15 expression vector pQE-9. (Qiagen, Inc., Chatsworth, CA). This plasmid vector encodes antibiotic resistance (Amp<sup>r</sup>), a bacterial origin of replication (ori), an IPTG-regulatable promoter/operator (P/O), a ribosome binding site (RBS), a 6-histidine tag (6-His), and restriction enzyme cloning sites.

The pQE-9 vector is digested with BamHI and XbaI and the amplified fragment is  
20 ligated into the pQE-9 vector maintaining the reading frame initiated at the bacterial RBS. The ligation mixture is then used to transform the E. coli strain M15/rep4 (Qiagen, Inc.) which contains multiple copies of the plasmid pREP4, which expresses the lacI repressor and also confers kanamycin resistance (Kan<sup>r</sup>). Transformants are identified by their ability to grow on LB plates and ampicillin/kanamycin resistant colonies are selected. Plasmid DNA is  
25 isolated and confirmed by restriction analysis.

Clones containing the desired constructs are grown overnight (O/N) in liquid culture in LB media supplemented with both Amp (100 ug/ml) and Kan (25 ug/ml). The O/N culture is used to inoculate a large culture at a ratio of 1:100 to 1:250. The cells are grown to an optical density 600 (O.D.<sup>600</sup>) of between 0.4 and 0.6. IPTG (Isopropyl-B-D-thiogalacto  
30 pyranoside) is then added to a final concentration of 1 mM. IPTG induces by inactivating the lacI repressor, clearing the P/O leading to increased gene expression.

Cells are grown for an extra 3 to 4 hours. Cells are then harvested by centrifugation (20 mins at 6000Xg). The cell pellet is solubilized in the chaotropic agent 6 Molar Guanidine HCl by stirring for 3-4 hours at 4°C. The cell debris is removed by centrifugation, and the supernatant containing the polypeptide is loaded onto a nickel-nitrilo-tri-acetic acid ("Ni-NTA") affinity resin column (available from QIAGEN, Inc., *supra*). Proteins with a 6 x His tag bind to the Ni-NTA resin with high affinity and can be purified in a simple one-step procedure (for details see: The QIAexpressionist (1995) QIAGEN, Inc., *supra*).

Briefly, the supernatant is loaded onto the column in 6 M guanidine-HCl, pH 8, the column is first washed with 10 volumes of 6 M guanidine-HCl, pH 8, then washed with 10 volumes of 6 M guanidine-HCl pH 6, and finally the polypeptide is eluted with 6 M guanidine-HCl, pH 5.

The purified protein is then renatured by dialyzing it against phosphate-buffered saline (PBS) or 50 mM Na-acetate, pH 6 buffer plus 200 mM NaCl. Alternatively, the protein can be successfully refolded while immobilized on the Ni-NTA column. The recommended conditions are as follows: renature using a linear 6M-1M urea gradient in 500 mM NaCl, 20% glycerol, 20 mM Tris/HCl pH 7.4, containing protease inhibitors. The renaturation should be performed over a period of 1.5 hours or more. After renaturation the proteins are eluted by the addition of 250 mM imidazole. Imidazole is removed by a final dialyzing step against PBS or 50 mM sodium acetate pH 6 buffer plus 200 mM NaCl. The purified protein is stored at 4°C or frozen at -80°C.

In addition to the above expression vector, the present invention further includes an expression vector comprising phage operator and promoter elements operatively linked to a polynucleotide of the present invention, called pHE4a. (ATCC Accession Number 209645, deposited on February 25, 1998.) This vector contains: 1) a neomycinphosphotransferase gene as a selection marker, 2) an E. coli origin of replication, 3) a T5 phage promoter sequence, 4) two lac operator sequences, 5) a Shine-Delgarno sequence, and 6) the lactose operon repressor gene (*lacIq*). The origin of replication (*oriC*) is derived from pUC19 (LTI, Gaithersburg, MD). The promoter sequence and operator sequences are made synthetically.

DNA can be inserted into the pHEa by restricting the vector with NdeI and XbaI, BamHI, XhoI, or Asp718, running the restricted product on a gel, and isolating the larger fragment (the stuffer fragment should be about 310 base pairs). The DNA insert is generated according to the PCR protocol described in Example 1, using PCR primers having restriction

sites for NdeI (5' primer) and XbaI, BamHI, XhoI, or Asp718 (3' primer). The PCR insert is gel purified and restricted with compatible enzymes. The insert and vector are ligated according to standard protocols.

The engineered vector could easily be substituted in the above protocol to express  
5 protein in a bacterial system.

***Example 6: Purification of a Polypeptide from an Inclusion Body***

The following alternative method can be used to purify a polypeptide expressed in *E*  
10 *coli* when it is present in the form of inclusion bodies. Unless otherwise specified, all of the following steps are conducted at 4-10°C.

Upon completion of the production phase of the *E. coli* fermentation, the cell culture is cooled to 4-10°C and the cells harvested by continuous centrifugation at 15,000 rpm (Heraeus Sepatech). On the basis of the expected yield of protein per unit weight of cell  
15 paste and the amount of purified protein required, an appropriate amount of cell paste, by weight, is suspended in a buffer solution containing 100 mM Tris, 50 mM EDTA, pH 7.4. The cells are dispersed to a homogeneous suspension using a high shear mixer.

The cells are then lysed by passing the solution through a microfluidizer (Microfluidics, Corp. or APV Gaulin, Inc.) twice at 4000-6000 psi. The homogenate is then  
20 mixed with NaCl solution to a final concentration of 0.5 M NaCl, followed by centrifugation at 7000 xg for 15 min. The resultant pellet is washed again using 0.5M NaCl, 100 mM Tris, 50 mM EDTA, pH 7.4.

The resulting washed inclusion bodies are solubilized with 1.5 M guanidine hydrochloride (GuHCl) for 2-4 hours. After 7000 xg centrifugation for 15 min., the pellet is  
25 discarded and the polypeptide containing supernatant is incubated at 4°C overnight to allow further GuHCl extraction.

Following high speed centrifugation (30,000 xg) to remove insoluble particles, the GuHCl solubilized protein is refolded by quickly mixing the GuHCl extract with 20 volumes of buffer containing 50 mM sodium, pH 4.5, 150 mM NaCl, 2 mM EDTA by vigorous  
30 stirring. The refolded diluted protein solution is kept at 4°C without mixing for 12 hours prior to further purification steps.

To clarify the refolded polypeptide solution, a previously prepared tangential filtration unit equipped with 0.16  $\mu\text{m}$  membrane filter with appropriate surface area (e.g., Filtron), equilibrated with 40 mM sodium acetate, pH 6.0 is employed. The filtered sample is loaded onto a cation exchange resin (e.g., Poros HS-50, Perseptive Biosystems). The column is washed with 40 mM sodium acetate, pH 6.0 and eluted with 250 mM, 500 mM, 1000 mM, and 1500 mM NaCl in the same buffer, in a stepwise manner. The absorbance at 280 nm of the effluent is continuously monitored. Fractions are collected and further analyzed by SDS-PAGE.

Fractions containing the polypeptide are then pooled and mixed with 4 volumes of water. The diluted sample is then loaded onto a previously prepared set of tandem columns of strong anion (Poros HQ-50, Perseptive Biosystems) and weak anion (Poros CM-20, Perseptive Biosystems) exchange resins. The columns are equilibrated with 40 mM sodium acetate, pH 6.0. Both columns are washed with 40 mM sodium acetate, pH 6.0, 200 mM NaCl. The CM-20 column is then eluted using a 10 column volume linear gradient ranging from 0.2 M NaCl, 50 mM sodium acetate, pH 6.0 to 1.0 M NaCl, 50 mM sodium acetate, pH 6.5. Fractions are collected under constant  $A_{280}$  monitoring of the effluent. Fractions containing the polypeptide (determined, for instance, by 16% SDS-PAGE) are then pooled.

The resultant polypeptide should exhibit greater than 95% purity after the above refolding and purification steps. No major contaminant bands should be observed from Commassie blue stained 16% SDS-PAGE gel when 5  $\mu\text{g}$  of purified protein is loaded. The purified protein can also be tested for endotoxin/LPS contamination, and typically the LPS content is less than 0.1 ng/ml according to LAL assays.

#### *Example 7: Cloning and Expression of a Polypeptide in a Baculovirus Expression System*

25

In this example, the plasmid shuttle vector pA2 is used to insert a polynucleotide into a baculovirus to express a polypeptide. This expression vector contains the strong polyhedrin promoter of the *Autographa californica* nuclear polyhedrosis virus (AcMNPV) followed by convenient restriction sites such as BamHI, Xba I and Asp718. The polyadenylation site of the simian virus 40 ("SV40") is used for efficient polyadenylation. For easy selection of recombinant virus, the plasmid contains the beta-galactosidase gene from *E. coli* under control of a weak *Drosophila* promoter in the same orientation, followed by the

30

polyadenylation signal of the polyhedrin gene. The inserted genes are flanked on both sides by viral sequences for cell-mediated homologous recombination with wild-type viral DNA to generate a viable virus that express the cloned polynucleotide.

Many other baculovirus vectors can be used in place of the vector above, such as pAc373, pVL941, and pAcIM1, as one skilled in the art would readily appreciate, as long as the construct provides appropriately located signals for transcription, translation, secretion and the like, including a signal peptide and an in-frame AUG as required. Such vectors are described, for instance, in Luckow et al., *Virology* 170:31-39 (1989).

Specifically, the cDNA sequence contained in the deposited clone, including the AUG initiation codon, is amplified using the PCR protocol described in Example 1. If a naturally occurring signal sequence is used to produce the polypeptide of the present invention, the pA2 vector does not need a second signal peptide. Alternatively, the vector can be modified (pA2 GP) to include a baculovirus leader sequence, using the standard methods described in Summers et al., "A Manual of Methods for Baculovirus Vectors and Insect Cell Culture Procedures," Texas Agricultural Experimental Station Bulletin No. 1555 (1987).

The amplified fragment is isolated from a 1% agarose gel using a commercially available kit ("GeneClean," BIO 101 Inc., La Jolla, Ca.). The fragment then is digested with appropriate restriction enzymes and again purified on a 1% agarose gel.

The plasmid is digested with the corresponding restriction enzymes and optionally, can be dephosphorylated using calf intestinal phosphatase, using routine procedures known in the art. The DNA is then isolated from a 1% agarose gel using a commercially available kit ("GeneClean" BIO 101 Inc., La Jolla, Ca.).

The fragment and the dephosphorylated plasmid are ligated together with T4 DNA ligase. *E. coli* HB101 or other suitable *E. coli* hosts such as XL-1 Blue (Stratagene Cloning Systems, La Jolla, CA) cells are transformed with the ligation mixture and spread on culture plates. Bacteria containing the plasmid are identified by digesting DNA from individual colonies and analyzing the digestion product by gel electrophoresis. The sequence of the cloned fragment is confirmed by DNA sequencing.

Five  $\mu$ g of a plasmid containing the polynucleotide is co-transfected with 1.0  $\mu$ g of a commercially available linearized baculovirus DNA ("BaculoGold™ baculovirus DNA", Pharmingen, San Diego, CA), using the lipofection method described by Felgner et al., *Proc.*

Natl. Acad. Sci. USA 84:7413-7417 (1987). One  $\mu\text{g}$  of BaculoGold™ virus DNA and 5  $\mu\text{g}$  of the plasmid are mixed in a sterile well of a microtiter plate containing 50  $\mu\text{l}$  of serum-free Grace's medium (Life Technologies Inc., Gaithersburg, MD). Afterwards, 10  $\mu\text{l}$  Lipofectin plus 90  $\mu\text{l}$  Grace's medium are added, mixed and incubated for 15 minutes at room temperature. Then the transfection mixture is added drop-wise to Sf9 insect cells (ATCC CRL 1711) seeded in a 35 mm tissue culture plate with 1 ml Grace's medium without serum. The plate is then incubated for 5 hours at 27° C. The transfection solution is then removed from the plate and 1 ml of Grace's insect medium supplemented with 10% fetal calf serum is added. Cultivation is then continued at 27° C for four days.

After four days the supernatant is collected and a plaque assay is performed, as described by Summers and Smith, *supra*. An agarose gel with "Blue Gal" (Life Technologies Inc., Gaithersburg) is used to allow easy identification and isolation of gal-expressing clones, which produce blue-stained plaques. (A detailed description of a "plaque assay" of this type can also be found in the user's guide for insect cell culture and baculovirology distributed by Life Technologies Inc., Gaithersburg, page 9-10.) After appropriate incubation, blue stained plaques are picked with the tip of a micropipettor (e.g., Eppendorf). The agar containing the recombinant viruses is then resuspended in a microcentrifuge tube containing 200  $\mu\text{l}$  of Grace's medium and the suspension containing the recombinant baculovirus is used to infect Sf9 cells seeded in 35 mm dishes. Four days later the supernatants of these culture dishes are harvested and then they are stored at 4° C.

To verify the expression of the polypeptide, Sf9 cells are grown in Grace's medium supplemented with 10% heat-inactivated FBS. The cells are infected with the recombinant baculovirus containing the polynucleotide at a multiplicity of infection ("MOI") of about 2. If radiolabeled proteins are desired, 6 hours later the medium is removed and is replaced with SF900 II medium minus methionine and cysteine (available from Life Technologies Inc., Rockville, MD). After 42 hours, 5  $\mu\text{Ci}$  of  $^{35}\text{S}$ -methionine and 5  $\mu\text{Ci}$   $^{35}\text{S}$ -cysteine (available from Amersham) are added. The cells are further incubated for 16 hours and then are harvested by centrifugation. The proteins in the supernatant as well as the intracellular proteins are analyzed by SDS-PAGE followed by autoradiography (if radiolabeled).

Microsequencing of the amino acid sequence of the amino terminus of purified protein may be used to determine the amino terminal sequence of the produced protein.



*Example 8: Expression of a Polypeptide in Mammalian Cells*

The polypeptide of the present invention can be expressed in a mammalian cell. A typical mammalian expression vector contains a promoter element, which mediates the initiation of transcription of mRNA, a protein coding sequence, and signals required for the termination of transcription and polyadenylation of the transcript. Additional elements include enhancers, Kozak sequences and intervening sequences flanked by donor and acceptor sites for RNA splicing. Highly efficient transcription is achieved with the early and late promoters from SV40, the long terminal repeats (LTRs) from Retroviruses, e.g., RSV, HTLV1, HIV1 and the early promoter of the cytomegalovirus (CMV). However, cellular elements can also be used (e.g., the human actin promoter).

Suitable expression vectors for use in practicing the present invention include, for example, vectors such as pSVL and pMSG (Pharmacia, Uppsala, Sweden), pRSVcat (ATCC 37152), pSV2dhfr (ATCC 37146), pBC12MI (ATCC 67109), pCMVSPORT 2.0, and pCMVSPORT 3.0. Mammalian host cells that could be used include, human Hela, 293, H9 and Jurkat cells, mouse NIH3T3 and C127 cells, Cos 1, Cos 7 and CV1, quail QC1-3 cells, mouse L cells and Chinese hamster ovary (CHO) cells.

Alternatively, the polypeptide can be expressed in stable cell lines containing the polynucleotide integrated into a chromosome. The co-transfection with a selectable marker such as DHFR, gpt, neomycin, hygromycin allows the identification and isolation of the transfected cells.

The transfected gene can also be amplified to express large amounts of the encoded protein. The DHFR (dihydrofolate reductase) marker is useful in developing cell lines that carry several hundred or even several thousand copies of the gene of interest. (See, e.g., Alt, F. W., et al., J. Biol. Chem. 253:1357-1370 (1978); Hamlin, J. L. and Ma, C., Biochem. et Biophys. Acta, 1097:107-143 (1990); Page, M. J. and Sydenham, M. A., Biotechnology 9:64-68 (1991).) Another useful selection marker is the enzyme glutamine synthase (GS) (Murphy et al., Biochem J. 227:277-279 (1991); Bebbington et al., Bio/Technology 10:169-175 (1992). Using these markers, the mammalian cells are grown in selective medium and the cells with the highest resistance are selected. These cell lines contain the amplified gene(s) integrated into a chromosome. Chinese hamster ovary (CHO) and NSO cells are often used for the production of proteins.

Derivatives of the plasmid pSV2-dhfr (ATCC Accession No. 37146), the expression vectors pC4 (ATCC Accession No. 209646) and pC6 (ATCC Accession No. 209647) contain the strong promoter (LTR) of the Rous Sarcoma Virus (Cullen et al., Molecular and Cellular Biology, 438-447 (March, 1985)) plus a fragment of the CMV-enhancer (Boshart et al., Cell 5 41:521-530 (1985).) Multiple cloning sites, e.g., with the restriction enzyme cleavage sites BamHI, XbaI and Asp718, facilitate the cloning of the gene of interest. The vectors also contain the 3' intron, the polyadenylation and termination signal of the rat preproinsulin gene, and the mouse DHFR gene under control of the SV40 early promoter.

Specifically, the plasmid pC6, for example, is digested with appropriate restriction 10 enzymes and then dephosphorylated using calf intestinal phosphates by procedures known in the art. The vector is then isolated from a 1% agarose gel.

A polynucleotide of the present invention is amplified according to the protocol outlined in Example 1. If a naturally occurring signal sequence is used to produce the polypeptide of the present invention, the vector does not need a second signal peptide. 15 Alternatively, if a naturally occurring signal sequence is not used, the vector can be modified to include a heterologous signal sequence. (See, e.g., WO 96/34891.)

The amplified fragment is isolated from a 1% agarose gel using a commercially available kit ("GeneClean," BIO 101 Inc., La Jolla, Ca.). The fragment then is digested with appropriate restriction enzymes and again purified on a 1% agarose gel.

20 The amplified fragment is then digested with the same restriction enzyme and purified on a 1% agarose gel. The isolated fragment and the dephosphorylated vector are then ligated with T4 DNA ligase. *E. coli* HB101 or XL-1 Blue cells are then transformed and bacteria are identified that contain the fragment inserted into plasmid pC6 using, for instance, restriction enzyme analysis.

25 Chinese hamster ovary cells lacking an active DHFR gene is used for transfection. Five µg of the expression plasmid pC6 or pC4 is cotransfected with 0.5 µg of the plasmid pSVneo using lipofectin (Felgner et al., *supra*). The plasmid pSV2-neo contains a dominant selectable marker, the *neo* gene from Tn5 encoding an enzyme that confers resistance to a group of antibiotics including G418. The cells are seeded in alpha minus MEM 30 supplemented with 1 mg/ml G418. After 2 days, the cells are trypsinized and seeded in hybridoma cloning plates (Greiner, Germany) in alpha minus MEM supplemented with 10, 25, or 50 ng/ml of methotrexate plus 1 mg/ml G418. After about 10-14 days single clones

are trypsinized and then seeded in 6-well petri dishes or 10 ml flasks using different concentrations of methotrexate (50 nM, 100 nM, 200 nM, 400 nM, 800 nM). Clones growing at the highest concentrations of methotrexate are then transferred to new 6-well plates containing even higher concentrations of methotrexate (1  $\mu$ M, 2  $\mu$ M, 5  $\mu$ M, 10 mM, 20 mM). The same procedure is repeated until clones are obtained which grow at a concentration of 100 - 200  $\mu$ M. Expression of the desired gene product is analyzed, for instance, by SDS-PAGE and Western blot or by reversed phase HPLC analysis.

#### *Example 9: Protein Fusions*

10

The polypeptides of the present invention are preferably fused to other proteins. These fusion proteins can be used for a variety of applications. For example, fusion of the present polypeptides to His-tag, HA-tag, protein A, IgG domains, and maltose binding protein facilitates purification. (See Example 5; see also EP A 394,827; Traunecker, et al., Nature 331:84-86 (1988).) Similarly, fusion to IgG-1, IgG-3, and albumin increases the halflife time in vivo. Nuclear localization signals fused to the polypeptides of the present invention can target the protein to a specific subcellular localization, while covalent heterodimer or homodimers can increase or decrease the activity of a fusion protein. Fusion proteins can also create chimeric molecules having more than one function. Finally, fusion proteins can increase solubility and/or stability of the fused protein compared to the non-fused protein. All of the types of fusion proteins described above can be made by modifying the following protocol, which outlines the fusion of a polypeptide to an IgG molecule, or the protocol described in Example 5.

Briefly, the human Fc portion of the IgG molecule can be PCR amplified, using primers that span the 5' and 3' ends of the sequence described below. These primers also should have convenient restriction enzyme sites that will facilitate cloning into an expression vector, preferably a mammalian expression vector.

For example, if pC4 (Accession No. 209646) is used, the human Fc portion can be ligated into the BamHI cloning site. Note that the 3' BamHI site should be destroyed. Next, the vector containing the human Fc portion is re-restricted with BamHI, linearizing the vector, and a polynucleotide of the present invention, isolated by the PCR protocol described in Example 1, is ligated into this BamHI site. Note that the polynucleotide is cloned without

a stop codon, otherwise a fusion protein will not be produced.

If the naturally occurring signal sequence is used to produce the polypeptide of the present invention, pC4 does not need a second signal peptide. Alternatively, if the naturally occurring signal sequence is not used, the vector can be modified to include a heterologous  
 5 signal sequence. (See, e.g., WO 96/34891.)

Human IgG Fc region:

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GGGATCCGGAGCCCAAATCTTCTGACAAAACCTCACACATGCCCACCGTGCCCAG
CACCTGAATTCGAGGGTGCACCGTCAGTCTTCTCTTCCCCCAAAACCCAAGGA
10 CACCCTCATGATCTCCCGGACTCCTGAGGTCACATGCGTGGTGGTGGACGTAAGC
CACGAAGACCCTGAGGTCAAGTTCAACTGGTACGTGGACGGCGTGGAGGTGCAT
AATGCCAAGACAAAGCCGCGGGAGGAGCAGTACAACAGCACGTACCGTGTGGTC
AGCGTCCTCACCGTCCTGCACCAGGACTGGCTGAATGGCAAGGAGTACAAGTGC
AAGGTCTCCAACAAAGCCCTCCCAACCCCCATCGAGAAAACCATCTCCAAAGCC
15 AAAGGGCAGCCCCGAGAACCACAGGTGTACACCCTGCCCCCATCCCGGGATGAG
CTGACCAAGAACCAGGTACGCCTGACCTGCCTGGTCAAAGGCTTCTATCCAAGC
GACATCGCCGTGGAGTGGGAGAGCAATGGGCAGCCGGAGAACAACACTACAAGAC
CACGCCTCCCGTGCTGGACTCCGACGGCTCCTTCTTCTCTACAGCAAGCTCACC
GTGGACAAGAGCAGGTGGCAGCAGGGGAACGTCTTCTCATGCTCCGTGATGCAT
20 GAGGCTCTGCACAACCACTACACGCAGAAGAGCCTCTCCCTGTCTCCGGGTAAAT
GAGTGCGACGGCCGCGACTCTAGAGGAT (SEQ ID NO:1685)
  
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*Example 10: Production of an Antibody from a Polypeptide*

25 **a) Hybridoma Technology**

The antibodies of the present invention can be prepared by a variety of methods. (See, Current Protocols, Chapter 2.) As one example of such methods, cells expressing polypeptide of the present invention are administered to an animal to induce the production of sera containing polyclonal antibodies. In a preferred method, a preparation of polypeptide  
 30 of the present invention is prepared and purified to render it substantially free of natural contaminants. Such a preparation is then introduced into an animal in order to produce polyclonal antisera of greater specific activity.

Monoclonal antibodies specific for polypeptide of the present invention are prepared using hybridoma technology. (Kohler et al., *Nature* 256:495 (1975); Kohler et al., *Eur. J. Immunol.* 6:511 (1976); Kohler et al., *Eur. J. Immunol.* 6:292 (1976); Hammerling et al., in: *Monoclonal Antibodies and T-Cell Hybridomas*, Elsevier, N.Y., pp. 563-681 (1981)). In  
5 general, an animal (preferably a mouse) is immunized with polypeptide of the present invention or, more preferably, with a secreted polypeptide of the present invention-expressing cell. Such polypeptide-expressing cells are cultured in any suitable tissue culture medium, preferably in Earle's modified Eagle's medium supplemented with 10% fetal bovine serum (inactivated at about 56°C), and supplemented with about 10 g/l of nonessential amino  
10 acids, about 1,000 U/ml of penicillin, and about 100 µg/ml of streptomycin.

The splenocytes of such mice are extracted and fused with a suitable myeloma cell line. Any suitable myeloma cell line may be employed in accordance with the present invention; however, it is preferable to employ the parent myeloma cell line (SP2O), available from the ATCC. After fusion, the resulting hybridoma cells are selectively maintained in  
15 HAT medium, and then cloned by limiting dilution as described by Wands et al. (*Gastroenterology* 80:225-232 (1981)). The hybridoma cells obtained through such a selection are then assayed to identify clones which secrete antibodies capable of binding the polypeptide of the present invention.

Alternatively, additional antibodies capable of binding to polypeptide of the present  
20 invention can be produced in a two-step procedure using anti-idiotypic antibodies. Such a method makes use of the fact that antibodies are themselves antigens, and therefore, it is possible to obtain an antibody which binds to a second antibody. In accordance with this method, protein specific antibodies are used to immunize an animal, preferably a mouse. The splenocytes of such an animal are then used to produce hybridoma cells, and the hybridoma  
25 cells are screened to identify clones which produce an antibody whose ability to bind to the polypeptide of the present invention-specific antibody can be blocked by polypeptide of the present invention. Such antibodies comprise anti-idiotypic antibodies to the polypeptide of the present invention-specific antibody and are used to immunize an animal to induce formation of further polypeptide of the present invention-specific antibodies.

30 For in vivo use of antibodies in humans, an antibody is "humanized". Such antibodies can be produced using genetic constructs derived from hybridoma cells producing the monoclonal antibodies described above. Methods for producing chimeric and humanized

antibodies are known in the art and are discussed herein. (See, for review, Morrison, Science 229:1202 (1985); Oi et al., BioTechniques 4:214 (1986); Cabilly et al., U.S. Patent No. 4,816,567; Taniguchi et al., EP 171496; Morrison et al., EP 173494; Neuberger et al., WO 8601533; Robinson et al., WO 8702671; Boulianne et al., Nature 312:643 (1984); Neuberger et al., Nature 314:268 (1985).)

**b) Isolation Of Antibody Fragments Directed Against Polypeptide of the Present Invention From A Library Of scFvs**

Naturally occurring V-genes isolated from human PBLs are constructed into a library of antibody fragments which contain reactivities against polypeptide of the present invention to which the donor may or may not have been exposed (see e.g., U.S. Patent 5,885,793 incorporated herein by reference in its entirety).

*Rescue of the Library.* A library of scFvs is constructed from the RNA of human PBLs as described in PCT publication WO 92/01047. To rescue phage displaying antibody fragments, approximately 10<sup>9</sup> E. coli harboring the phagemid are used to inoculate 50 ml of 2xTY containing 1% glucose and 100 µg/ml of ampicillin (2xTY-AMP-GLU) and grown to an O.D. of 0.8 with shaking. Five ml of this culture is used to inoculate 50 ml of 2xTY-AMP-GLU, 2 x 10<sup>8</sup> TU of delta gene 3 helper (M13 delta gene III, see PCT publication WO 92/01047) are added and the culture incubated at 37°C for 45 minutes without shaking and then at 37°C for 45 minutes with shaking. The culture is centrifuged at 4000 r.p.m. for 10 min. and the pellet resuspended in 2 liters of 2xTY containing 100 µg/ml ampicillin and 50 µg/ml kanamycin and grown overnight. Phage are prepared as described in PCT publication WO 92/01047.

M13 delta gene III is prepared as follows: M13 delta gene III helper phage does not encode gene III protein, hence the phage(mid) displaying antibody fragments have a greater avidity of binding to antigen. Infectious M13 delta gene III particles are made by growing the helper phage in cells harboring a pUC19 derivative supplying the wild type gene III protein during phage morphogenesis. The culture is incubated for 1 hour at 37° C without shaking and then for a further hour at 37°C with shaking. Cells are spun down (IEC-Centra 8,400 r.p.m. for 10 min), resuspended in 300 ml 2xTY broth containing 100 µg ampicillin/ml and 25 µg kanamycin/ml (2xTY-AMP-KAN) and grown overnight, shaking at 37°C. Phage particles are purified and concentrated from the culture medium by two PEG-precipitations

(Sambrook et al., 1990), resuspended in 2 ml PBS and passed through a 0.45  $\mu$ m filter (Minisart NML; Sartorius) to give a final concentration of approximately 10<sup>13</sup> transducing units/ml (ampicillin-resistant clones).

*Panning of the Library.* Immunotubes (Nunc) are coated overnight in PBS with 4 ml of either 100  $\mu$ g/ml or 10  $\mu$ g/ml of a polypeptide of the present invention. Tubes are blocked with 2% Marvel-PBS for 2 hours at 37°C and then washed 3 times in PBS. Approximately 10<sup>13</sup> TU of phage is applied to the tube and incubated for 30 minutes at room temperature tumbling on an over and under turntable and then left to stand for another 1.5 hours. Tubes are washed 10 times with PBS 0.1% Tween-20 and 10 times with PBS. Phage are eluted by adding 1 ml of 100 mM triethylamine and rotating 15 minutes on an under and over turntable after which the solution is immediately neutralized with 0.5 ml of 1.0M Tris-HCl, pH 7.4. Phage are then used to infect 10 ml of mid-log E. coli TG1 by incubating eluted phage with bacteria for 30 minutes at 37°C. The E. coli are then plated on TYE plates containing 1% glucose and 100  $\mu$ g/ml ampicillin. The resulting bacterial library is then rescued with delta gene 3 helper phage as described above to prepare phage for a subsequent round of selection. This process is then repeated for a total of 4 rounds of affinity purification with tube-washing increased to 20 times with PBS, 0.1% Tween-20 and 20 times with PBS for rounds 3 and 4.

*Characterization of Binders.* Eluted phage from the 3rd and 4th rounds of selection are used to infect E. coli HB 2151 and soluble scFv is produced (Marks, et al., 1991) from single colonies for assay. ELISAs are performed with microtitre plates coated with either 10 pg/ml of the polypeptide of the present invention in 50 mM bicarbonate pH 9.6. Clones positive in ELISA are further characterized by PCR fingerprinting (see, e.g., PCT publication WO 92/01047) and then by sequencing. These ELISA positive clones may also be further characterized by techniques known in the art, such as, for example, epitope mapping, binding affinity, receptor signal transduction, ability to block or competitively inhibit antibody/antigen binding, and competitive agonistic or antagonistic activity.

*Example 11: Method of Determining Alterations in a Gene Corresponding to a Polynucleotide*

RNA isolated from entire families or individual patients presenting with a phenotype of interest (such as a disease) is be isolated. cDNA is then generated from these RNA samples using protocols known in the art. (See, Sambrook.) The cDNA is then used as a template for PCR, employing primers surrounding regions of interest in SEQ ID NO:X;  
5 and/or the nucleotide sequence of the related cDNA in the cDNA clone contained in a deposited library. Suggested PCR conditions consist of 35 cycles at 95 degrees C for 30 seconds; 60-120 seconds at 52-58 degrees C; and 60-120 seconds at 70 degrees C, using buffer solutions described in Sidransky et al., Science 252:706 (1991).

PCR products are then sequenced using primers labeled at their 5' end with T4  
10 polynucleotide kinase, employing SequiTherm Polymerase. (Epicentre Technologies). The intron-exon borders of selected exons is also determined and genomic PCR products analyzed to confirm the results. PCR products harboring suspected mutations is then cloned and sequenced to validate the results of the direct sequencing.

PCR products is cloned into T-tailed vectors as described in Holton et al., Nucleic  
15 Acids Research, 19:1156 (1991) and sequenced with T7 polymerase (United States Biochemical). Affected individuals are identified by mutations not present in unaffected individuals.

Genomic rearrangements are also observed as a method of determining alterations in a gene corresponding to a polynucleotide. Genomic clones isolated according to Example 2  
20 are nick-translated with digoxigenindeoxy-uridine 5'-triphosphate (Boehringer Mannheim), and FISH performed as described in Johnson et al., Methods Cell Biol. 35:73-99 (1991). Hybridization with the labeled probe is carried out using a vast excess of human cot-1 DNA for specific hybridization to the corresponding genomic locus.

Chromosomes are counterstained with 4,6-diamino-2-phenylidole and propidium  
25 iodide, producing a combination of C- and R-bands. Aligned images for precise mapping are obtained using a triple-band filter set (Chroma Technology, Brattleboro, VT) in combination with a cooled charge-coupled device camera (Photometrics, Tucson, AZ) and variable excitation wavelength filters. (Johnson et al., Genet. Anal. Tech. Appl., 8:75 (1991).) Image collection, analysis and chromosomal fractional length measurements are performed using  
30 the ISee Graphical Program System. (Inovision Corporation, Durham, NC.) Chromosome alterations of the genomic region hybridized by the probe are identified as insertions, deletions, and translocations. These alterations are used as a diagnostic marker for an



associated disease.

*Example 12: Method of Detecting Abnormal Levels of a Polypeptide in a Biological Sample*

5           A polypeptide of the present invention can be detected in a biological sample, and if an increased or decreased level of the polypeptide is detected, this polypeptide is a marker for a particular phenotype. Methods of detection are numerous, and thus, it is understood that one skilled in the art can modify the following assay to fit their particular needs.

          For example, antibody-sandwich ELISAs are used to detect polypeptides in a sample,  
10       preferably a biological sample. Wells of a microtiter plate are coated with specific antibodies, at a final concentration of 0.2 to 10 ug/ml. The antibodies are either monoclonal or polyclonal and are produced by the method described in Example 10. The wells are blocked so that non-specific binding of the polypeptide to the well is reduced.

          The coated wells are then incubated for > 2 hours at RT with a sample containing the  
15       polypeptide. Preferably, serial dilutions of the sample should be used to validate results. The plates are then washed three times with deionized or distilled water to remove unbounded polypeptide.

          Next, 50 ul of specific antibody-alkaline phosphatase conjugate, at a concentration of 25-400 ng, is added and incubated for 2 hours at room temperature. The plates are again  
20       washed three times with deionized or distilled water to remove unbounded conjugate.

          Add 75 ul of 4-methylumbelliferyl phosphate (MUP) or p-nitrophenyl phosphate (NPP) substrate solution to each well and incubate 1 hour at room temperature. Measure the reaction by a microtiter plate reader. Prepare a standard curve, using serial dilutions of a control sample, and plot polypeptide concentration on the X-axis (log scale) and fluorescence  
25       or absorbance of the Y-axis (linear scale). Interpolate the concentration of the polypeptide in the sample using the standard curve.

*Example 13: Formulation*

30       The invention also provides methods of treatment and/or prevention of diseases or disorders (such as, for example, any one or more of the diseases or disorders disclosed

herein) by administration to a subject of an effective amount of a Therapeutic. By therapeutic is meant a polynucleotides or polypeptides of the invention (including fragments and variants), agonists or antagonists thereof, and/or antibodies thereto, in combination with a pharmaceutically acceptable carrier type (e.g., a sterile carrier).

5           The Therapeutic will be formulated and dosed in a fashion consistent with good medical practice, taking into account the clinical condition of the individual patient (especially the side effects of treatment with the Therapeutic alone), the site of delivery, the method of administration, the scheduling of administration, and other factors known to practitioners. The "effective amount" for purposes herein is thus determined by such  
10 considerations.

As a general proposition, the total pharmaceutically effective amount of the Therapeutic administered parenterally per dose will be in the range of about 1 µg/kg/day to 10 mg/kg/day of patient body weight, although, as noted above, this will be subject to therapeutic discretion. More preferably, this dose is at least 0.01 mg/kg/day, and most  
15 preferably for humans between about 0.01 and 1 mg/kg/day for the hormone. If given continuously, the Therapeutic is typically administered at a dose rate of about 1 µg/kg/hour to about 50 µg/kg/hour, either by 1-4 injections per day or by continuous subcutaneous infusions, for example, using a mini-pump. An intravenous bag solution may also be employed. The length of treatment needed to observe changes and the interval following  
20 treatment for responses to occur appears to vary depending on the desired effect.

Therapeutics can be administered orally, rectally, parenterally, intracisternally, intravaginally, intraperitoneally, topically (as by powders, ointments, gels, drops or transdermal patch), buccally, or as an oral or nasal spray. "Pharmaceutically acceptable carrier" refers to a non-toxic solid, semisolid or liquid filler, diluent, encapsulating material  
25 or formulation auxiliary of any. The term "parenteral" as used herein refers to modes of administration which include intravenous, intramuscular, intraperitoneal, intrasternal, subcutaneous and intraarticular injection and infusion.

Therapeutics of the invention are also suitably administered by sustained-release systems. Suitable examples of sustained-release Therapeutics are administered orally,  
30 rectally, parenterally, intracisternally, intravaginally, intraperitoneally, topically (as by powders, ointments, gels, drops or transdermal patch), buccally, or as an oral or nasal spray. "Pharmaceutically acceptable carrier" refers to a non-toxic solid, semisolid or liquid filler,

diluent, encapsulating material or formulation auxiliary of any type. The term "parenteral" as used herein refers to modes of administration which include intravenous, intramuscular, intraperitoneal, intrasternal, subcutaneous and intraarticular injection and infusion.

Therapeutics of the invention are also suitably administered by sustained-release systems. Suitable examples of sustained-release Therapeutics include suitable polymeric materials (such as, for example, semi-permeable polymer matrices in the form of shaped articles, e.g., films, or microcapsules), suitable hydrophobic materials (for example as an emulsion in an acceptable oil) or ion exchange resins, and sparingly soluble derivatives (such as, for example, a sparingly soluble salt).

Sustained-release matrices include polylactides (U.S. Pat. No. 3,773,919, EP 58,481), copolymers of L-glutamic acid and gamma-ethyl-L-glutamate (Sidman et al., *Biopolymers* 22:547-556 (1983)), poly (2- hydroxyethyl methacrylate) (Langer et al., *J. Biomed. Mater. Res.* 15:167-277 (1981), and Langer, *Chem. Tech.* 12:98-105 (1982)), ethylene vinyl acetate (Langer et al., *Id.*) or poly-D- (-)-3-hydroxybutyric acid (EP 133,988).

Sustained-release Therapeutics also include liposomally entrapped Therapeutics of the invention (*see* generally, Langer, *Science* 249:1527-1533 (1990); Treat et al., in *Liposomes in the Therapy of Infectious Disease and Cancer*, Lopez-Berestein and Fidler (eds.), Liss, New York, pp. 317 -327 and 353-365 (1989)). Liposomes containing the Therapeutic are prepared by methods known per se: DE 3,218,121; Epstein et al., *Proc. Natl. Acad. Sci. (USA)* 82:3688-3692 (1985); Hwang et al., *Proc. Natl. Acad. Sci.(USA)* 77:4030-4034 (1980); EP 52,322; EP 36,676; EP 88,046; EP 143,949; EP 142,641; Japanese Pat. Appl. 83-118008; U.S. Pat. Nos. 4,485,045 and 4,544,545; and EP 102,324. Ordinarily, the liposomes are of the small (about 200-800 Angstroms) unilamellar type in which the lipid content is greater than about 30 mol. percent cholesterol, the selected proportion being adjusted for the optimal Therapeutic.

In yet an additional embodiment, the Therapeutics of the invention are delivered by way of a pump (*see* Langer, *supra*; Sefton, *CRC Crit. Ref. Biomed. Eng.* 14:201 (1987); Buchwald et al., *Surgery* 88:507 (1980); Saudek et al., *N. Engl. J. Med.* 321:574 (1989)).

Other controlled release systems are discussed in the review by Langer (*Science* 249:1527-1533 (1990)).

For parenteral administration, in one embodiment, the Therapeutic is formulated generally by mixing it at the desired degree of purity, in a unit dosage injectable form

(solution, suspension, or emulsion), with a pharmaceutically acceptable carrier, i.e., one that is non-toxic to recipients at the dosages and concentrations employed and is compatible with other ingredients of the formulation. For example, the formulation preferably does not include oxidizing agents and other compounds that are known to be deleterious to the

5 Therapeutic.

Generally, the formulations are prepared by contacting the Therapeutic uniformly and intimately with liquid carriers or finely divided solid carriers or both. Then, if necessary, the product is shaped into the desired formulation. Preferably the carrier is a parenteral carrier, more preferably a solution that is isotonic with the blood of the recipient. Examples of such

10 carrier vehicles include water, saline, Ringer's solution, and dextrose solution. Non-aqueous vehicles such as fixed oils and ethyl oleate are also useful herein, as well as liposomes.

The carrier suitably contains minor amounts of additives such as substances that enhance isotonicity and chemical stability. Such materials are non-toxic to recipients at the dosages and concentrations employed, and include buffers such as phosphate, citrate,

15 succinate, acetic acid, and other organic acids or their salts; antioxidants such as ascorbic acid; low molecular weight (less than about ten residues) polypeptides, e.g., polyarginine or tripeptides; proteins, such as serum albumin, gelatin, or immunoglobulins; hydrophilic polymers such as polyvinylpyrrolidone; amino acids, such as glycine, glutamic acid, aspartic acid, or arginine; monosaccharides, disaccharides, and other carbohydrates including

20 cellulose or its derivatives, glucose, manose, or dextrans; chelating agents such as EDTA; sugar alcohols such as mannitol or sorbitol; counterions such as sodium; and/or nonionic surfactants such as polysorbates, poloxamers, or PEG.

The Therapeutic is typically formulated in such vehicles at a concentration of about 0.1 mg/ml to 100 mg/ml, preferably 1-10 mg/ml, at a pH of about 3 to 8. It will be

25 understood that the use of certain of the foregoing excipients, carriers, or stabilizers will result in the formation of polypeptide salts.

Any pharmaceutical used for therapeutic administration can be sterile. Sterility is readily accomplished by filtration through sterile filtration membranes (e.g., 0.2 micron membranes). Therapeutics generally are placed into a container having a sterile access port,

30 for example, an intravenous solution bag or vial having a stopper pierceable by a hypodermic injection needle.

Therapeutics ordinarily will be stored in unit or multi-dose containers, for example,

sealed ampoules or vials, as an aqueous solution or as a lyophilized formulation for reconstitution. As an example of a lyophilized formulation, 10-ml vials are filled with 5 ml of sterile-filtered 1% (w/v) aqueous Therapeutic solution, and the resulting mixture is lyophilized. The infusion solution is prepared by reconstituting the lyophilized Therapeutic  
5 using bacteriostatic Water-for-Injection.

The invention also provides a pharmaceutical pack or kit comprising one or more containers filled with one or more of the ingredients of the Therapeutics of the invention. Associated with such container(s) can be a notice in the form prescribed by a governmental agency regulating the manufacture, use or sale of pharmaceuticals or biological products,  
10 which notice reflects approval by the agency of manufacture, use or sale for human administration. In addition, the Therapeutics may be employed in conjunction with other therapeutic compounds.

The Therapeutics of the invention may be administered alone or in combination with adjuvants. Adjuvants that may be administered with the Therapeutics of the invention  
15 include, but are not limited to, alum, alum plus deoxycholate (ImmunoAg), MTP-PE (Biocine Corp.), QS21 (Genentech, Inc.), BCG, and MPL. In a specific embodiment, Therapeutics of the invention are administered in combination with alum. In another specific embodiment, Therapeutics of the invention are administered in combination with QS-21. Further adjuvants that may be administered with the Therapeutics of the invention include,  
20 but are not limited to, Monophosphoryl lipid immunomodulator, AdjuVax 100a, QS-21, QS-18, CRL1005, Aluminum salts, MF-59, and Virosomal adjuvant technology. Vaccines that may be administered with the Therapeutics of the invention include, but are not limited to, vaccines directed toward protection against MMR (measles, mumps, rubella), polio, varicella, tetanus/diphtheria, hepatitis A, hepatitis B, haemophilus influenzae B, whooping  
25 cough, pneumonia, influenza, Lyme's Disease, rotavirus, cholera, yellow fever, Japanese encephalitis, poliomyelitis, rabies, typhoid fever, and pertussis. Combinations may be administered either concomitantly, e.g., as an admixture, separately but simultaneously or concurrently; or sequentially. This includes presentations in which the combined agents are administered together as a therapeutic mixture, and also procedures in which the combined  
30 agents are administered separately but simultaneously, e.g., as through separate intravenous lines into the same individual. Administration "in combination" further includes the separate administration of one of the compounds or agents given first, followed by the second.

The Therapeutics of the invention may be administered alone or in combination with other therapeutic agents. Therapeutic agents that may be administered in combination with the Therapeutics of the invention, include but not limited to, other members of the TNF family, chemotherapeutic agents, antibiotics, steroidal and non-steroidal anti-inflammatories, conventional immunotherapeutic agents, cytokines and/or growth factors. Combinations may be administered either concomitantly, e.g., as an admixture, separately but simultaneously or concurrently; or sequentially. This includes presentations in which the combined agents are administered together as a therapeutic mixture, and also procedures in which the combined agents are administered separately but simultaneously, e.g., as through separate intravenous lines into the same individual. Administration "in combination" further includes the separate administration of one of the compounds or agents given first, followed by the second.

In one embodiment, the Therapeutics of the invention are administered in combination with members of the TNF family. TNF, TNF-related or TNF-like molecules that may be administered with the Therapeutics of the invention include, but are not limited to, soluble forms of TNF-alpha, lymphotoxin-alpha (LT-alpha, also known as TNF-beta), LT-beta (found in complex heterotrimer LT-alpha2-beta), OPGL, FasL, CD27L, CD30L, CD40L, 4-1BBL, DcR3, OX40L, TNF-gamma (International Publication No. WO 96/14328), AIM-I (International Publication No. WO 97/33899), endokine-alpha (International Publication No. WO 98/07880), TR6 (International Publication No. WO 98/30694), OPG, and neutrokin-alpha (International Publication No. WO 98/18921, OX40, and nerve growth factor (NGF), and soluble forms of Fas, CD30, CD27, CD40 and 4-1BB, TR2 (International Publication No. WO 96/34095), DR3 (International Publication No. WO 97/33904), DR4 (International Publication No. WO 98/32856), TR5 (International Publication No. WO 98/30693), TR6 (International Publication No. WO 98/30694), TR7 (International Publication No. WO 98/41629), TRANK, TR9 (International Publication No. WO 98/56892), TR10 (International Publication No. WO 98/54202), 312C2 (International Publication No. WO 98/06842), and TR12, and soluble forms CD154, CD70, and CD153.

In certain embodiments, Therapeutics of the invention are administered in combination with antiretroviral agents, nucleoside reverse transcriptase inhibitors, non-nucleoside reverse transcriptase inhibitors, and/or protease inhibitors. Nucleoside reverse transcriptase inhibitors that may be administered in combination with the Therapeutics of the invention, include, but are not limited to, RETROVIR™ (zidovudine/AZT), VIDEX™

(didanosine/ddI), HIVID™ (zalcitabine/ddC), ZERIT™ (stavudine/d4T), EPIVIR™ (lamivudine/3TC), and COMBIVIR™ (zidovudine/lamivudine). Non-nucleoside reverse transcriptase inhibitors that may be administered in combination with the Therapeutics of the invention, include, but are not limited to, VIRAMUNE™ (nevirapine), RESCRIPTOR™ (delavirdine), and SUSTIVA™ (efavirenz). Protease inhibitors that may be administered in combination with the Therapeutics of the invention, include, but are not limited to, CRIXIVAN™ (indinavir), NORVIR™ (ritonavir), INVIRASE™ (saquinavir), and VIRACEPT™ (nelfinavir). In a specific embodiment, antiretroviral agents, nucleoside reverse transcriptase inhibitors, non-nucleoside reverse transcriptase inhibitors, and/or protease inhibitors may be used in any combination with Therapeutics of the invention to treat AIDS and/or to prevent or treat HIV infection.

In other embodiments, Therapeutics of the invention may be administered in combination with anti-opportunistic infection agents. Anti-opportunistic agents that may be administered in combination with the Therapeutics of the invention, include, but are not limited to, TRIMETHOPRIM-SULFAMETHOXAZOLE™, DAPSONE™, PENTAMIDINE™, ATOVAQUONE™, ISONIAZID™, RIFAMPIN™, PYRAZINAMIDE™, ETHAMBUTOL™, RIFABUTIN™, CLARITHROMYCIN™, AZITHROMYCIN™, GANCICLOVIR™, FOSCARNET™, CIDOFOVIR™, FLUCONAZOLE™, ITRACONAZOLE™, KETOCONAZOLE™, ACYCLOVIR™, FAMCICLOVIR™, PYRIMETHAMINE™, LEUCOVORIN™, NEUPOGEN™ (filgrastim/G-CSF), and LEUKINE™ (sargramostim/GM-CSF). In a specific embodiment, Therapeutics of the invention are used in any combination with TRIMETHOPRIM-SULFAMETHOXAZOLE™, DAPSONE™, PENTAMIDINE™, and/or ATOVAQUONE™ to prophylactically treat or prevent an opportunistic *Pneumocystis carinii* pneumonia infection. In another specific embodiment, Therapeutics of the invention are used in any combination with ISONIAZID™, RIFAMPIN™, PYRAZINAMIDE™, and/or ETHAMBUTOL™ to prophylactically treat or prevent an opportunistic *Mycobacterium avium* complex infection. In another specific embodiment, Therapeutics of the invention are used in any combination with RIFABUTIN™, CLARITHROMYCIN™, and/or AZITHROMYCIN™ to prophylactically treat or prevent an opportunistic *Mycobacterium tuberculosis* infection. In another specific embodiment, Therapeutics of the invention are used in any combination with GANCICLOVIR™,

FOSCARNET™, and/or CIDOFOVIR™ to prophylactically treat or prevent an opportunistic cytomegalovirus infection. In another specific embodiment, Therapeutics of the invention are used in any combination with FLUCONAZOLE™, ITRACONAZOLE™, and/or KETOCONAZOLE™ to prophylactically treat or prevent an opportunistic fungal infection.

5 In another specific embodiment, Therapeutics of the invention are used in any combination with ACYCLOVIR™ and/or FAMCICOLVIR™ to prophylactically treat or prevent an opportunistic herpes simplex virus type I and/or type II infection. In another specific embodiment, Therapeutics of the invention are used in any combination with PYRIMETHAMINE™ and/or LEUCOVORIN™ to prophylactically treat or prevent an

10 opportunistic *Toxoplasma gondii* infection. In another specific embodiment, Therapeutics of the invention are used in any combination with LEUCOVORIN™ and/or NEUPOGEN™ to prophylactically treat or prevent an opportunistic bacterial infection.

In a further embodiment, the Therapeutics of the invention are administered in combination with an antiviral agent. Antiviral agents that may be administered with the

15 Therapeutics of the invention include, but are not limited to, acyclovir, ribavirin, amantadine, and remantidine.

In a further embodiment, the Therapeutics of the invention are administered in combination with an antibiotic agent. Antibiotic agents that may be administered with the Therapeutics of the invention include, but are not limited to, amoxicillin, beta-lactamases,

20 aminoglycosides, beta-lactam (glycopeptide), beta-lactamases, Clindamycin, chloramphenicol, cephalosporins, ciprofloxacin, ciprofloxacin, erythromycin, fluoroquinolones, macrolides, metronidazole, penicillins, quinolones, rifampin, streptomycin, sulfonamide, tetracyclines, trimethoprim, trimethoprim-sulfamthoxazole, and vancomycin.

Conventional nonspecific immunosuppressive agents, that may be administered in

25 combination with the Therapeutics of the invention include, but are not limited to, steroids, cyclosporine, cyclosporine analogs, cyclophosphamide methylprednisone, prednisone, azathioprine, FK-506, 15-deoxyspergualin, and other immunosuppressive agents that act by suppressing the function of responding T cells.

In specific embodiments, Therapeutics of the invention are administered in

30 combination with immunosuppressants. Immunosuppressants preparations that may be administered with the Therapeutics of the invention include, but are not limited to, ORTHOCLONE™ (OKT3), SANDIMMUNE™/NEORAL™/SANGDYA™ (cyclosporin),



PROGRAF™ (tacrolimus), CELLCEPT™ (mycophenolate), Azathioprine, glucocorticosteroids, and RAPAMUNE™ (sirolimus). In a specific embodiment, immunosuppressants may be used to prevent rejection of organ or bone marrow transplantation.

In an additional embodiment, Therapeutics of the invention are administered alone or  
5 in combination with one or more intravenous immune globulin preparations. Intravenous immune globulin preparations that may be administered with the Therapeutics of the invention include, but not limited to, GAMMAR™, IVEEGAM™, SANDOGLOBULIN™, GAMMAGARD S/D™, and GAMIMUNE™. In a specific embodiment, Therapeutics of the invention are administered in combination with intravenous immune globulin preparations in  
10 transplantation therapy (e.g., bone marrow transplant).

In an additional embodiment, the Therapeutics of the invention are administered alone or in combination with an anti-inflammatory agent. Anti-inflammatory agents that may be administered with the Therapeutics of the invention include, but are not limited to, glucocorticoids and the nonsteroidal anti-inflammatories, aminoarylcarboxylic acid  
15 derivatives, arylacetic acid derivatives, arylbutyric acid derivatives, arylcarboxylic acids, arylpropionic acid derivatives, pyrazoles, pyrazolones, salicylic acid derivatives, thiazinecarboxamides, e-acetamidocaproic acid, S-adenosylmethionine, 3-amino-4-hydroxybutyric acid, amixetrine, bendazac, benzydamine, bucolome, difenpiramide, ditazol, emorfazone, guaiazulene, nabumetone, nimesulide, orgotein, oxaceprol, paranyline,  
20 perisoxal, pifoxime, proquazone, proxazole, and tenidap.

In another embodiment, compositions of the invention are administered in combination with a chemotherapeutic agent. Chemotherapeutic agents that may be administered with the Therapeutics of the invention include, but are not limited to, antibiotic derivatives (e.g., doxorubicin, bleomycin, daunorubicin, and dactinomycin); antiestrogens  
25 (e.g., tamoxifen); antimetabolites (e.g., fluorouracil, 5-FU, methotrexate, floxuridine, interferon alpha-2b, glutamic acid, plicamycin, mercaptopurine, and 6-thioguanine); cytotoxic agents (e.g., carmustine, BCNU, lomustine, CCNU, cytosine arabinoside, cyclophosphamide, estramustine, hydroxyurea, procarbazine, mitomycin, busulfan, cis-platin, and vincristine sulfate); hormones (e.g., medroxyprogesterone, estramustine phosphate  
30 sodium, ethinyl estradiol, estradiol, megestrol acetate, methyltestosterone, diethylstilbestrol diphosphate, chlorotrianisene, and testolactone); nitrogen mustard derivatives (e.g., mephallen, chorambucil, mechlorethamine (nitrogen mustard) and thiotepa); steroids and

combinations (e.g., bethamethasone sodium phosphate); and others (e.g., dicarbazine, asparaginase, mitotane, vincristine sulfate, vinblastine sulfate, and etoposide).

In a specific embodiment, Therapeutics of the invention are administered in combination with CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) or  
5 any combination of the components of CHOP. In another embodiment, Therapeutics of the invention are administered in combination with Rituximab. In a further embodiment, Therapeutics of the invention are administered with Rituxmab and CHOP, or Rituxmab and any combination of the components of CHOP.

In an additional embodiment, the Therapeutics of the invention are administered in  
10 combination with cytokines. Cytokines that may be administered with the Therapeutics of the invention include, but are not limited to, IL2, IL3, IL4, IL5, IL6, IL7, IL10, IL12, IL13, IL15, anti-CD40, CD40L, IFN-gamma and TNF-alpha. In another embodiment, Therapeutics of the invention may be administered with any interleukin, including, but not limited to, IL-1alpha, IL-1beta, IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, IL-8, IL-9, IL-10, IL-11,  
15 IL-12, IL-13, IL-14, IL-15, IL-16, IL-17, IL-18, IL-19, IL-20, and IL-21.

In an additional embodiment, the Therapeutics of the invention are administered in combination with angiogenic proteins. Angiogenic proteins that may be administered with the Therapeutics of the invention include, but are not limited to, Glioma Derived Growth Factor (GDGF), as disclosed in European Patent Number EP-399816; Platelet Derived  
20 Growth Factor-A (PDGF-A), as disclosed in European Patent Number EP-682110; Platelet Derived Growth Factor-B (PDGF-B), as disclosed in European Patent Number EP-282317; Placental Growth Factor (PIGF), as disclosed in International Publication Number WO 92/06194; Placental Growth Factor-2 (PIGF-2), as disclosed in Hauser et al., Growth Factors, 4:259-268 (1993); Vascular Endothelial Growth Factor (VEGF), as disclosed in International  
25 Publication Number WO 90/13649; Vascular Endothelial Growth Factor-A (VEGF-A), as disclosed in European Patent Number EP-506477; Vascular Endothelial Growth Factor-2 (VEGF-2), as disclosed in International Publication Number WO 96/39515; Vascular Endothelial Growth Factor B (VEGF-3); Vascular Endothelial Growth Factor B-186 (VEGF-B186), as disclosed in International Publication Number WO 96/26736; Vascular Endothelial  
30 Growth Factor-D (VEGF-D), as disclosed in International Publication Number WO 98/02543; Vascular Endothelial Growth Factor-D (VEGF-D), as disclosed in International Publication Number WO 98/07832; and Vascular Endothelial Growth Factor-E (VEGF-E), as

disclosed in German Patent Number DE19639601. The above mentioned references are incorporated herein by reference herein.

In an additional embodiment, the Therapeutics of the invention are administered in combination with hematopoietic growth factors. Hematopoietic growth factors that may be administered with the Therapeutics of the invention include, but are not limited to, LEUKINE™ (SARGRAMOSTIM™) and NEUPOGEN™ (FILGRASTIM™).

In an additional embodiment, the Therapeutics of the invention are administered in combination with Fibroblast Growth Factors. Fibroblast Growth Factors that may be administered with the Therapeutics of the invention include, but are not limited to, FGF-1, FGF-2, FGF-3, FGF-4, FGF-5, FGF-6, FGF-7, FGF-8, FGF-9, FGF-10, FGF-11, FGF-12, FGF-13, FGF-14, and FGF-15.

In additional embodiments, the Therapeutics of the invention are administered in combination with other therapeutic or prophylactic regimens, such as, for example, radiation therapy.

#### *Example 14: Method of Treating Decreased Levels of the Polypeptide*

The present invention relates to a method for treating an individual in need of an increased level of a polypeptide of the invention in the body comprising administering to such an individual a composition comprising a therapeutically effective amount of an agonist of the invention (including polypeptides of the invention). Moreover, it will be appreciated that conditions caused by a decrease in the standard or normal expression level of a polypeptide of the present invention in an individual can be treated by administering the agonist or antagonist of the present invention. Thus, the invention also provides a method of treatment of an individual in need of an increased level of the polypeptide comprising administering to such an individual a Therapeutic comprising an amount of the agonist or antagonist to increase the activity level of the polypeptide in such an individual.

For example, a patient with decreased levels of a polypeptide receives a daily dose 0.1-100 ug/kg of the agonist or antagonist for six consecutive days. The exact details of the dosing scheme, based on administration and formulation, are provided in Example 13.

#### *Example 15: Method of Treating Increased Levels of the Polypeptide*

The present invention also relates to a method of treating an individual in need of a decreased level of a polypeptide of the invention in the body comprising administering to such an individual a composition comprising a therapeutically effective amount of an antagonist of the invention (including polypeptides and antibodies of the invention).

In one example, antisense technology is used to inhibit production of a polypeptide of the present invention. This technology is one example of a method of decreasing levels of a polypeptide, due to a variety of etiologies, such as cancer.

For example, a patient diagnosed with abnormally increased levels of a polypeptide is administered intravenously antisense polynucleotides at 0.5, 1.0, 1.5, 2.0 and 3.0 mg/kg day for 21 days. This treatment is repeated after a 7-day rest period if the treatment was well tolerated. The formulation of the antisense polynucleotide is provided in Example 13.

*Example 16: Method of Treatment Using Gene Therapy-Ex Vivo*

15

One method of gene therapy transplants fibroblasts, which are capable of expressing a polypeptide, onto a patient. Generally, fibroblasts are obtained from a subject by skin biopsy. The resulting tissue is placed in tissue-culture medium and separated into small pieces. Small chunks of the tissue are placed on a wet surface of a tissue culture flask, approximately ten pieces are placed in each flask. The flask is turned upside down, closed tight and left at room temperature over night. After 24 hours at room temperature, the flask is inverted and the chunks of tissue remain fixed to the bottom of the flask and fresh media (e.g., Ham's F12 media, with 10% FBS, penicillin and streptomycin) is added. The flasks are then incubated at 37 degree C for approximately one week.

25 At this time, fresh media is added and subsequently changed every several days. After an additional two weeks in culture, a monolayer of fibroblasts emerge. The monolayer is trypsinized and scaled into larger flasks.

pMV-7 (Kirschmeier, P.T. et al., DNA, 7:219-25 (1988)), flanked by the long terminal repeats of the Moloney murine sarcoma virus, is digested with EcoRI and HindIII and subsequently treated with calf intestinal phosphatase. The linear vector is fractionated on agarose gel and purified, using glass beads.

30 The cDNA encoding a polypeptide of the present invention can be amplified using

PCR primers which correspond to the 5' and 3' end sequences respectively as set forth in Example 1 using primers and having appropriate restriction sites and initiation/stop codons, if necessary. Preferably, the 5' primer contains an EcoRI site and the 3' primer includes a HindIII site. Equal quantities of the Moloney murine sarcoma virus linear backbone and the amplified EcoRI and HindIII fragment are added together, in the presence of T4 DNA ligase. The resulting mixture is maintained under conditions appropriate for ligation of the two fragments. The ligation mixture is then used to transform bacteria HB101, which are then plated onto agar containing kanamycin for the purpose of confirming that the vector has the gene of interest properly inserted.

The amphotropic pA317 or GP+am12 packaging cells are grown in tissue culture to confluent density in Dulbecco's Modified Eagles Medium (DMEM) with 10% calf serum (CS), penicillin and streptomycin. The MSV vector containing the gene is then added to the media and the packaging cells transduced with the vector. The packaging cells now produce infectious viral particles containing the gene (the packaging cells are now referred to as producer cells).

Fresh media is added to the transduced producer cells, and subsequently, the media is harvested from a 10 cm plate of confluent producer cells. The spent media, containing the infectious viral particles, is filtered through a millipore filter to remove detached producer cells and this media is then used to infect fibroblast cells. Media is removed from a sub-confluent plate of fibroblasts and quickly replaced with the media from the producer cells. This media is removed and replaced with fresh media. If the titer of virus is high, then virtually all fibroblasts will be infected and no selection is required. If the titer is very low, then it is necessary to use a retroviral vector that has a selectable marker, such as neo or his. Once the fibroblasts have been efficiently infected, the fibroblasts are analyzed to determine whether protein is produced.

The engineered fibroblasts are then transplanted onto the host, either alone or after having been grown to confluence on cytodex 3 microcarrier beads.

*Example 17: Gene Therapy Using Endogenous Genes Corresponding To Polynucleotides of the Invention*

Another method of gene therapy according to the present invention involves operably

associating the endogenous polynucleotide sequence of the invention with a promoter via homologous recombination as described, for example, in U.S. Patent NO: 5,641,670, issued June 24, 1997; International Publication NO: WO 96/29411, published September 26, 1996; International Publication NO: WO 94/12650, published August 4, 1994; Koller et al., *Proc. Natl. Acad. Sci. USA*, 86:8932-8935 (1989); and Zijlstra et al., *Nature*, 342:435-438 (1989). This method involves the activation of a gene which is present in the target cells, but which is not expressed in the cells, or is expressed at a lower level than desired.

Polynucleotide constructs are made which contain a promoter and targeting sequences, which are homologous to the 5' non-coding sequence of endogenous polynucleotide sequence, flanking the promoter. The targeting sequence will be sufficiently near the 5' end of the polynucleotide sequence so the promoter will be operably linked to the endogenous sequence upon homologous recombination. The promoter and the targeting sequences can be amplified using PCR. Preferably, the amplified promoter contains distinct restriction enzyme sites on the 5' and 3' ends. Preferably, the 3' end of the first targeting sequence contains the same restriction enzyme site as the 5' end of the amplified promoter and the 5' end of the second targeting sequence contains the same restriction site as the 3' end of the amplified promoter.

The amplified promoter and the amplified targeting sequences are digested with the appropriate restriction enzymes and subsequently treated with calf intestinal phosphatase. The digested promoter and digested targeting sequences are added together in the presence of T4 DNA ligase. The resulting mixture is maintained under conditions appropriate for ligation of the two fragments. The construct is size fractionated on an agarose gel then purified by phenol extraction and ethanol precipitation.

In this Example, the polynucleotide constructs are administered as naked polynucleotides via electroporation. However, the polynucleotide constructs may also be administered with transfection-facilitating agents, such as liposomes, viral sequences, viral particles, precipitating agents, etc. Such methods of delivery are known in the art.

Once the cells are transfected, homologous recombination will take place which results in the promoter being operably linked to the endogenous polynucleotide sequence. This results in the expression of polynucleotide corresponding to the polynucleotide in the cell. Expression may be detected by immunological staining, or any other method known in the art.

Fibroblasts are obtained from a subject by skin biopsy. The resulting tissue is placed in DMEM + 10% fetal calf serum. Exponentially growing or early stationary phase fibroblasts are trypsinized and rinsed from the plastic surface with nutrient medium. An aliquot of the cell suspension is removed for counting, and the remaining cells are subjected to centrifugation. The supernatant is aspirated and the pellet is resuspended in 5 ml of electroporation buffer (20 mM HEPES pH 7.3, 137 mM NaCl, 5 mM KCl, 0.7 mM Na<sub>2</sub>HPO<sub>4</sub>, 6 mM dextrose). The cells are recentrifuged, the supernatant aspirated, and the cells resuspended in electroporation buffer containing 1 mg/ml acetylated bovine serum albumin. The final cell suspension contains approximately  $3 \times 10^6$  cells/ml. Electroporation should be performed immediately following resuspension.

Plasmid DNA is prepared according to standard techniques. For example, to construct a plasmid for targeting to the locus corresponding to the polynucleotide of the invention, plasmid pUC18 (MBI Fermentas, Amherst, NY) is digested with HindIII. The CMV promoter is amplified by PCR with an XbaI site on the 5' end and a BamHI site on the 3' end. Two non-coding sequences are amplified via PCR: one non-coding sequence (fragment 1) is amplified with a HindIII site at the 5' end and an Xba site at the 3' end; the other non-coding sequence (fragment 2) is amplified with a BamHI site at the 5' end and a HindIII site at the 3' end. The CMV promoter and the fragments (1 and 2) are digested with the appropriate enzymes (CMV promoter - XbaI and BamHI; fragment 1 - XbaI; fragment 2 - BamHI) and ligated together. The resulting ligation product is digested with HindIII, and ligated with the HindIII-digested pUC18 plasmid.

Plasmid DNA is added to a sterile cuvette with a 0.4 cm electrode gap (Bio-Rad). The final DNA concentration is generally at least 120 µg/ml. 0.5 ml of the cell suspension (containing approximately  $1.5 \times 10^6$  cells) is then added to the cuvette, and the cell suspension and DNA solutions are gently mixed. Electroporation is performed with a Gene-Pulser apparatus (Bio-Rad). Capacitance and voltage are set at 960 µF and 250-300 V, respectively. As voltage increases, cell survival decreases, but the percentage of surviving cells that stably incorporate the introduced DNA into their genome increases dramatically. Given these parameters, a pulse time of approximately 14-20 mSec should be observed.

Electroporated cells are maintained at room temperature for approximately 5 min, and the contents of the cuvette are then gently removed with a sterile transfer pipette. The cells are added directly to 10 ml of prewarmed nutrient media (DMEM with 15% calf serum) in a

10 cm dish and incubated at 37 degree C. The following day, the media is aspirated and replaced with 10 ml of fresh media and incubated for a further 16-24 hours.

The engineered fibroblasts are then injected into the host, either alone or after having been grown to confluence on cytodex 3 microcarrier beads. The fibroblasts now produce the protein product. The fibroblasts can then be introduced into a patient as described above.

*Example 18: Method of Treatment Using Gene Therapy - In Vivo*

Another aspect of the present invention is using *in vivo* gene therapy methods to treat disorders, diseases and conditions. The gene therapy method relates to the introduction of naked nucleic acid (DNA, RNA, and antisense DNA or RNA) sequences into an animal to increase or decrease the expression of the polypeptide. The polynucleotide of the present invention may be operatively linked to a promoter or any other genetic elements necessary for the expression of the polypeptide by the target tissue. Such gene therapy and delivery techniques and methods are known in the art, see, for example, WO90/11092, WO98/11779; U.S. Patent NO. 5693622, 5705151, 5580859; Tabata et al., Cardiovasc. Res. 35(3):470-479 (1997); Chao et al., Pharmacol. Res. 35(6):517-522 (1997); Wolff, Neuromuscul. Disord. 7(5):314-318 (1997); Schwartz et al., Gene Ther. 3(5):405-411 (1996); Tsurumi et al., Circulation 94(12):3281-3290 (1996) (incorporated herein by reference).

The polynucleotide constructs may be delivered by any method that delivers injectable materials to the cells of an animal, such as, injection into the interstitial space of tissues (heart, muscle, skin, lung, liver, intestine and the like). The polynucleotide constructs can be delivered in a pharmaceutically acceptable liquid or aqueous carrier.

The term "naked" polynucleotide, DNA or RNA, refers to sequences that are free from any delivery vehicle that acts to assist, promote, or facilitate entry into the cell, including viral sequences, viral particles, liposome formulations, lipofectin or precipitating agents and the like. However, the polynucleotides of the present invention may also be delivered in liposome formulations (such as those taught in Felgner P.L. et al. (1995) Ann. NY Acad. Sci. 772:126-139 and Abdallah B. et al. (1995) Biol. Cell 85(1):1-7) which can be prepared by methods well known to those skilled in the art.

The polynucleotide vector constructs used in the gene therapy method are preferably constructs that will not integrate into the host genome nor will they contain sequences that



allow for replication. Any strong promoter known to those skilled in the art can be used for driving the expression of DNA. Unlike other gene therapies techniques, one major advantage of introducing naked nucleic acid sequences into target cells is the transitory nature of the polynucleotide synthesis in the cells. Studies have shown that non-replicating DNA sequences can be introduced into cells to provide production of the desired polypeptide for periods of up to six months.

The polynucleotide construct can be delivered to the interstitial space of tissues within the an animal, including of muscle, skin, brain, lung, liver, spleen, bone marrow, thymus, heart, lymph, blood, bone, cartilage, pancreas, kidney, gall bladder, stomach, intestine, testis, ovary, uterus, rectum, nervous system, eye, gland, and connective tissue. Interstitial space of the tissues comprises the intercellular fluid, mucopolysaccharide matrix among the reticular fibers of organ tissues, elastic fibers in the walls of vessels or chambers, collagen fibers of fibrous tissues, or that same matrix within connective tissue ensheathing muscle cells or in the lacunae of bone. It is similarly the space occupied by the plasma of the circulation and the lymph fluid of the lymphatic channels. Delivery to the interstitial space of muscle tissue is preferred for the reasons discussed below. They may be conveniently delivered by injection into the tissues comprising these cells. They are preferably delivered to and expressed in persistent, non-dividing cells which are differentiated, although delivery and expression may be achieved in non-differentiated or less completely differentiated cells, such as, for example, stem cells of blood or skin fibroblasts. *In vivo* muscle cells are particularly competent in their ability to take up and express polynucleotides.

For the naked polynucleotide injection, an effective dosage amount of DNA or RNA will be in the range of from about 0.05 g/kg body weight to about 50 mg/kg body weight. Preferably the dosage will be from about 0.005 mg/kg to about 20 mg/kg and more preferably from about 0.05 mg/kg to about 5 mg/kg. Of course, as the artisan of ordinary skill will appreciate, this dosage will vary according to the tissue site of injection. The appropriate and effective dosage of nucleic acid sequence can readily be determined by those of ordinary skill in the art and may depend on the condition being treated and the route of administration. The preferred route of administration is by the parenteral route of injection into the interstitial space of tissues. However, other parenteral routes may also be used, such as, inhalation of an aerosol formulation particularly for delivery to lungs or bronchial tissues, throat or mucous membranes of the nose. In addition, naked polynucleotide constructs can be delivered to

arteries during angioplasty by the catheter used in the procedure.

The dose response effects of injected polynucleotide in muscle *in vivo* is determined as follows. Suitable template DNA for production of mRNA coding for polypeptide of the present invention is prepared in accordance with a standard recombinant DNA methodology.

- 5 The template DNA, which may be either circular or linear, is either used as naked DNA or complexed with liposomes. The quadriceps muscles of mice are then injected with various amounts of the template DNA.

- 10 Five to six week old female and male Balb/C mice are anesthetized by intraperitoneal injection with 0.3 ml of 2.5% Avertin. A 1.5 cm incision is made on the anterior thigh, and the quadriceps muscle is directly visualized. The template DNA is injected in 0.1 ml of carrier in a 1 cc syringe through a 27 gauge needle over one minute, approximately 0.5 cm from the distal insertion site of the muscle into the knee and about 0.2 cm deep. A suture is placed over the injection site for future localization, and the skin is closed with stainless steel clips.

- 15 After an appropriate incubation time (e.g., 7 days) muscle extracts are prepared by excising the entire quadriceps. Every fifth 15  $\mu$ m cross-section of the individual quadriceps muscles is histochemically stained for protein expression. A time course for protein expression may be done in a similar fashion except that quadriceps from different mice are harvested at different times. Persistence of DNA in muscle following injection may be determined by Southern blot analysis after preparing total cellular DNA and HIRT supernatants from injected and control mice. The results of the above experimentation in mice can be used to extrapolate proper dosages and other treatment parameters in humans and other animals using naked DNA.

25 *Example 19: Transgenic Animals*

- The polypeptides of the invention can also be expressed in transgenic animals. Animals of any species, including, but not limited to, mice, rats, rabbits, hamsters, guinea pigs, pigs, micro-pigs, goats, sheep, cows and non-human primates, e.g., baboons, monkeys, and chimpanzees may be used to generate transgenic animals. In a specific embodiment, techniques described herein or otherwise known in the art, are used to express polypeptides of the invention in humans, as part of a gene therapy protocol.
- 30

Any technique known in the art may be used to introduce the transgene (*i.e.*, polynucleotides of the invention) into animals to produce the founder lines of transgenic animals. Such techniques include, but are not limited to, pronuclear microinjection (Paterson et al., Appl. Microbiol. Biotechnol. 40:691-698 (1994); Carver et al., Biotechnology (NY) 11:1263-1270 (1993); Wright et al., Biotechnology (NY) 9:830-834 (1991); and Hoppe et al., U.S. Pat. No. 4,873,191 (1989)); retrovirus mediated gene transfer into germ lines (Van der Putten et al., Proc. Natl. Acad. Sci., USA 82:6148-6152 (1985)), blastocysts or embryos; gene targeting in embryonic stem cells (Thompson et al., Cell 56:313-321 (1989)); electroporation of cells or embryos (Lo, 1983, Mol Cell. Biol. 3:1803-1814 (1983)); introduction of the polynucleotides of the invention using a gene gun (see, *e.g.*, Ulmer et al., Science 259:1745 (1993); introducing nucleic acid constructs into embryonic pluripotent stem cells and transferring the stem cells back into the blastocyst; and sperm-mediated gene transfer (Lavitrano et al., Cell 57:717-723 (1989); etc. For a review of such techniques, see Gordon, "Transgenic Animals," Intl. Rev. Cytol. 115:171-229 (1989), which is incorporated by reference herein in its entirety.

Any technique known in the art may be used to produce transgenic clones containing polynucleotides of the invention, for example, nuclear transfer into enucleated oocytes of nuclei from cultured embryonic, fetal, or adult cells induced to quiescence (Campell et al., Nature 380:64-66 (1996); Wilmut et al., Nature 385:810-813 (1997)).

The present invention provides for transgenic animals that carry the transgene in all their cells, as well as animals which carry the transgene in some, but not all their cells, *i.e.*, mosaic animals or chimeric. The transgene may be integrated as a single transgene or as multiple copies such as in concatamers, *e.g.*, head-to-head tandems or head-to-tail tandems. The transgene may also be selectively introduced into and activated in a particular cell type by following, for example, the teaching of Lasko et al. (Lasko et al., Proc. Natl. Acad. Sci. USA 89:6232-6236 (1992)). The regulatory sequences required for such a cell-type specific activation will depend upon the particular cell type of interest, and will be apparent to those of skill in the art. When it is desired that the polynucleotide transgene be integrated into the chromosomal site of the endogenous gene, gene targeting is preferred. Briefly, when such a technique is to be utilized, vectors containing some nucleotide sequences homologous to the endogenous gene are designed for the purpose of integrating, via homologous recombination with chromosomal sequences, into and disrupting the function of the nucleotide sequence of

the endogenous gene. The transgene may also be selectively introduced into a particular cell type, thus inactivating the endogenous gene in only that cell type, by following, for example, the teaching of Gu et al. (Gu et al., Science 265:103-106 (1994)). The regulatory sequences required for such a cell-type specific inactivation will depend upon the particular cell type of interest, and will be apparent to those of skill in the art.

Once transgenic animals have been generated, the expression of the recombinant gene may be assayed utilizing standard techniques. Initial screening may be accomplished by Southern blot analysis or PCR techniques to analyze animal tissues to verify that integration of the transgene has taken place. The level of mRNA expression of the transgene in the tissues of the transgenic animals may also be assessed using techniques which include, but are not limited to, Northern blot analysis of tissue samples obtained from the animal, *in situ* hybridization analysis, and reverse transcriptase-PCR (rt-PCR). Samples of transgenic gene-expressing tissue may also be evaluated immunocytochemically or immunohistochemically using antibodies specific for the transgene product.

Once the founder animals are produced, they may be bred, inbred, outbred, or crossbred to produce colonies of the particular animal. Examples of such breeding strategies include, but are not limited to: outbreeding of founder animals with more than one integration site in order to establish separate lines; inbreeding of separate lines in order to produce compound transgenics that express the transgene at higher levels because of the effects of additive expression of each transgene; crossing of heterozygous transgenic animals to produce animals homozygous for a given integration site in order to both augment expression and eliminate the need for screening of animals by DNA analysis; crossing of separate homozygous lines to produce compound heterozygous or homozygous lines; and breeding to place the transgene on a distinct background that is appropriate for an experimental model of interest.

Transgenic animals of the invention have uses which include, but are not limited to, animal model systems useful in elaborating the biological function of polypeptides of the present invention, studying conditions and/or disorders associated with aberrant expression, and in screening for compounds effective in ameliorating such conditions and/or disorders.

#### *Example 20: Knock-Out Animals*

Endogenous gene expression can also be reduced by inactivating or "knocking out" the gene and/or its promoter using targeted homologous recombination. (E.g., see Smithies et al., *Nature* 317:230-234 (1985); Thomas & Capecchi, *Cell* 51:503-512 (1987); Thompson et al., *Cell* 5:313-321 (1989); each of which is incorporated by reference herein in its entirety). For example, a mutant, non-functional polynucleotide of the invention (or a completely unrelated DNA sequence) flanked by DNA homologous to the endogenous polynucleotide sequence (either the coding regions or regulatory regions of the gene) can be used, with or without a selectable marker and/or a negative selectable marker, to transfect cells that express polypeptides of the invention *in vivo*. In another embodiment, techniques known in the art are used to generate knockouts in cells that contain, but do not express the gene of interest. Insertion of the DNA construct, via targeted homologous recombination, results in inactivation of the targeted gene. Such approaches are particularly suited in research and agricultural fields where modifications to embryonic stem cells can be used to generate animal offspring with an inactive targeted gene (e.g., see Thomas & Capecchi 1987 and Thompson 1989, *supra*). However this approach can be routinely adapted for use in humans provided the recombinant DNA constructs are directly administered or targeted to the required site *in vivo* using appropriate viral vectors that will be apparent to those of skill in the art.

In further embodiments of the invention, cells that are genetically engineered to express the polypeptides of the invention, or alternatively, that are genetically engineered not to express the polypeptides of the invention (e.g., knockouts) are administered to a patient *in vivo*. Such cells may be obtained from the patient (i.e., animal, including human) or an MHC compatible donor and can include, but are not limited to fibroblasts, bone marrow cells, blood cells (e.g., lymphocytes), adipocytes, muscle cells, endothelial cells etc. The cells are genetically engineered *in vitro* using recombinant DNA techniques to introduce the coding sequence of polypeptides of the invention into the cells, or alternatively, to disrupt the coding sequence and/or endogenous regulatory sequence associated with the polypeptides of the invention, e.g., by transduction (using viral vectors, and preferably vectors that integrate the transgene into the cell genome) or transfection procedures, including, but not limited to, the use of plasmids, cosmids, YACs, naked DNA, electroporation, liposomes, etc. The coding sequence of the polypeptides of the invention can be placed under the control of a strong constitutive or inducible promoter or promoter/enhancer to achieve expression, and

preferably secretion, of the polypeptides of the invention. The engineered cells which express and preferably secrete the polypeptides of the invention can be introduced into the patient systemically, e.g., in the circulation, or intraperitoneally.

Alternatively, the cells can be incorporated into a matrix and implanted in the body, e.g., genetically engineered fibroblasts can be implanted as part of a skin graft; genetically engineered endothelial cells can be implanted as part of a lymphatic or vascular graft. (See, for example, Anderson et al. U.S. Patent No. 5,399,349; and Mulligan & Wilson, U.S. Patent No. 5,460,959 each of which is incorporated by reference herein in its entirety).

When the cells to be administered are non-autologous or non-MHC compatible cells, they can be administered using well known techniques which prevent the development of a host immune response against the introduced cells. For example, the cells may be introduced in an encapsulated form which, while allowing for an exchange of components with the immediate extracellular environment, does not allow the introduced cells to be recognized by the host immune system.

Transgenic and "knock-out" animals of the invention have uses which include, but are not limited to, animal model systems useful in elaborating the biological function of polypeptides of the present invention, studying conditions and/or disorders associated with aberrant expression, and in screening for compounds effective in ameliorating such conditions and/or disorders.

20

*Example 22: Assays Detecting Stimulation or Inhibition of B cell Proliferation and Differentiation*

Generation of functional humoral immune responses requires both soluble and cognate signaling between B-lineage cells and their microenvironment. Signals may impart a positive stimulus that allows a B-lineage cell to continue its programmed development, or a negative stimulus that instructs the cell to arrest its current developmental pathway. To date, numerous stimulatory and inhibitory signals have been found to influence B cell responsiveness including IL-2, IL-4, IL-5, IL-6, IL-7, IL10, IL-13, IL-14 and IL-15. Interestingly, these signals are by themselves weak effectors but can, in combination with various co-stimulatory proteins, induce activation, proliferation, differentiation, homing, tolerance and death among B cell populations.

One of the best studied classes of B-cell co-stimulatory proteins is the TNF-superfamily. Within this family CD40, CD27, and CD30 along with their respective ligands CD154, CD70, and CD153 have been found to regulate a variety of immune responses. Assays which allow for the detection and/or observation of the proliferation and differentiation of these B-cell populations and their precursors are valuable tools in determining the effects various proteins may have on these B-cell populations in terms of proliferation and differentiation. Listed below are two assays designed to allow for the detection of the differentiation, proliferation, or inhibition of B-cell populations and their precursors.

**In Vitro Assay-** Agonists or antagonists of the invention can be assessed for its ability to induce activation, proliferation, differentiation or inhibition and/or death in B-cell populations and their precursors. The activity of the agonists or antagonists of the invention on purified human tonsillar B cells, measured qualitatively over the dose range from 0.1 to 10,000 ng/mL, is assessed in a standard B-lymphocyte co-stimulation assay in which purified tonsillar B cells are cultured in the presence of either formalin-fixed *Staphylococcus aureus* Cowan I (SAC) or immobilized anti-human IgM antibody as the priming agent. Second signals such as IL-2 and IL-15 synergize with SAC and IgM crosslinking to elicit B cell proliferation as measured by tritiated-thymidine incorporation. Novel synergizing agents can be readily identified using this assay. The assay involves isolating human tonsillar B cells by magnetic bead (MACS) depletion of CD3-positive cells. The resulting cell population is greater than 95% B cells as assessed by expression of CD45R(B220).

Various dilutions of each sample are placed into individual wells of a 96-well plate to which are added  $10^5$  B-cells suspended in culture medium (RPMI 1640 containing 10% FBS,  $5 \times 10^{-5}$  M 2ME, 100U/ml penicillin, 10ug/ml streptomycin, and  $10^{-5}$  dilution of SAC) in a total volume of 150ul. Proliferation or inhibition is quantitated by a 20h pulse (1uCi/well) with 3H-thymidine (6.7 Ci/mM) beginning 72h post factor addition. The positive and negative controls are IL2 and medium respectively.

**In Vivo Assay-** BALB/c mice are injected (i.p.) twice per day with buffer only, or 2 mg/Kg of agonists or antagonists of the invention, or truncated forms thereof. Mice receive this treatment for 4 consecutive days, at which time they are sacrificed and various tissues and serum collected for analyses. Comparison of H&E sections from normal spleens and spleens treated with agonists or antagonists of the invention identify the results of the activity

of the agonists or antagonists on spleen cells, such as the diffusion of peri-arterial lymphatic sheaths, and/or significant increases in the nucleated cellularity of the red pulp regions, which may indicate the activation of the differentiation and proliferation of B-cell populations. Immunohistochemical studies using a B cell marker, anti-CD45R(B220), are used to  
5 determine whether any physiological changes to splenic cells, such as splenic disorganization, are due to increased B-cell representation within loosely defined B-cell zones that infiltrate established T-cell regions.

Flow cytometric analyses of the spleens from mice treated with agonist or antagonist is used to indicate whether the agonists or antagonists specifically increases the proportion of  
10 ThB+, CD45R(B220)dull B cells over that which is observed in control mice. Likewise, a predicted consequence of increased mature B-cell representation in vivo is a relative increase in serum Ig titers. Accordingly, serum IgM and IgA levels are compared between buffer and agonists or antagonists-treated mice.

The studies described in this example tested activity of agonists or antagonists of the  
15 invention. However, one skilled in the art could easily modify the exemplified studies to test the activity of polynucleotides or polypeptides of the invention (e.g., gene therapy).

#### *Example 23: T Cell Proliferation Assay*

20 A CD3-induced proliferation assay is performed on PBMCs and is measured by the uptake of <sup>3</sup>H-thymidine. The assay is performed as follows. Ninety-six well plates are coated with 100 µl/well of mAb to CD3 (HIT3a, Pharmingen) or isotype-matched control mAb (B33.1) overnight at 4 degrees C (1 µg/ml in .05M bicarbonate buffer, pH 9.5), then washed three times with PBS. PBMC are isolated by F/H gradient centrifugation from  
25 human peripheral blood and added to quadruplicate wells (5 x 10<sup>4</sup>/well) of mAb coated plates in RPMI containing 10% FCS and P/S in the presence of varying concentrations of agonists or antagonists of the invention (total volume 200 µl). Relevant protein buffer and medium alone are controls. After 48 hr. culture at 37 degrees C, plates are spun for 2 min. at 1000 rpm and 100 µl of supernatant is removed and stored -20 degrees C for measurement of IL-2  
30 (or other cytokines) if effect on proliferation is observed. Wells are supplemented with 100 µl of medium containing 0.5 uCi of <sup>3</sup>H-thymidine and cultured at 37 degrees C for 18-24 hr. Wells are harvested and incorporation of <sup>3</sup>H-thymidine used as a measure of proliferation.



Anti-CD3 alone is the positive control for proliferation. IL-2 (100 U/ml) is also used as a control which enhances proliferation. Control antibody which does not induce proliferation of T cells is used as the negative controls for the effects of agonists or antagonists of the invention.

- 5           The studies described in this example tested activity of agonists or antagonists of the invention. However, one skilled in the art could easily modify the exemplified studies to test the activity of polynucleotides or polypeptides of the invention (e.g., gene therapy).

10           *Example 24: Effect of Agonists or Antagonists of the Invention on the Expression of MHC Class II, Costimulatory and Adhesion Molecules and Cell Differentiation of Monocytes and Monocyte-Derived Human Dendritic Cells*

- 15           Dendritic cells are generated by the expansion of proliferating precursors found in the peripheral blood: adherent PBMC or elutriated monocytic fractions are cultured for 7-10 days with GM-CSF (50 ng/ml) and IL-4 (20 ng/ml). These dendritic cells have the characteristic phenotype of immature cells (expression of CD1, CD80, CD86, CD40 and MHC class II antigens). Treatment with activating factors, such as TNF- $\alpha$ , causes a rapid change in surface phenotype (increased expression of MHC class I and II, costimulatory and adhesion molecules, downregulation of FC $\gamma$ RII, upregulation of CD83). These changes correlate with
- 20           increased antigen-presenting capacity and with functional maturation of the dendritic cells.

- FACS analysis of surface antigens is performed as follows. Cells are treated 1-3 days with increasing concentrations of agonist or antagonist of the invention or LPS (positive control), washed with PBS containing 1% BSA and 0.02 mM sodium azide, and then incubated with 1:20 dilution of appropriate FITC- or PE-labeled monoclonal antibodies for
- 25           30 minutes at 4 degrees C. After an additional wash, the labeled cells are analyzed by flow cytometry on a FACScan (Becton Dickinson).

- Effect on the production of cytokines. Cytokines generated by dendritic cells, in particular IL-12, are important in the initiation of T-cell dependent immune responses. IL-12 strongly
- 30           influences the development of Th1 helper T-cell immune response, and induces cytotoxic T and NK cell function. An ELISA is used to measure the IL-12 release as follows. Dendritic cells ( $10^6$ /ml) are treated with increasing concentrations of agonists or antagonists of the

invention for 24 hours. LPS (100 ng/ml) is added to the cell culture as positive control. Supernatants from the cell cultures are then collected and analyzed for IL-12 content using commercial ELISA kit (e.g, R & D Systems (Minneapolis, MN)). The standard protocols provided with the kits are used.

5

Effect on the expression of MHC Class II, costimulatory and adhesion molecules. Three major families of cell surface antigens can be identified on monocytes: adhesion molecules, molecules involved in antigen presentation, and Fc receptor. Modulation of the expression of MHC class II antigens and other costimulatory molecules, such as B7 and ICAM-1, may result in changes in the antigen presenting capacity of monocytes and ability to induce T cell activation. Increase expression of Fc receptors may correlate with improved monocyte cytotoxic activity, cytokine release and phagocytosis.

10

FACS analysis is used to examine the surface antigens as follows. Monocytes are treated 1-5 days with increasing concentrations of agonists or antagonists of the invention or LPS (positive control), washed with PBS containing 1% BSA and 0.02 mM sodium azide, and then incubated with 1:20 dilution of appropriate FITC- or PE-labeled monoclonal antibodies for 30 minutes at 4 degreesC. After an additional wash, the labeled cells are analyzed by flow cytometry on a FACScan (Becton Dickinson).

15

Monocyte activation and/or increased survival. Assays for molecules that activate (or alternatively, inactivate) monocytes and/or increase monocyte survival (or alternatively, decrease monocyte survival) are known in the art and may routinely be applied to determine whether a molecule of the invention functions as an inhibitor or activator of monocytes. Agonists or antagonists of the invention can be screened using the three assays described below. For each of these assays, Peripheral blood mononuclear cells (PBMC) are purified from single donor leukopacks (American Red Cross, Baltimore, MD) by centrifugation through a Histopaque gradient (Sigma). Monocytes are isolated from PBMC by counterflow centrifugal elutriation.

20

25

Monocyte Survival Assay. Human peripheral blood monocytes progressively lose viability when cultured in absence of serum or other stimuli. Their death results from internally regulated process (apoptosis). Addition to the culture of activating factors, such as TNF-alpha

30

dramatically improves cell survival and prevents DNA fragmentation. Propidium iodide (PI) staining is used to measure apoptosis as follows. Monocytes are cultured for 48 hours in polypropylene tubes in serum-free medium (positive control), in the presence of 100 ng/ml TNF-alpha (negative control), and in the presence of varying concentrations of the compound to be tested. Cells are suspended at a concentration of  $2 \times 10^6$ /ml in PBS containing PI at a final concentration of 5  $\mu$ g/ml, and then incubated at room temperature for 5 minutes before FACSscan analysis. PI uptake has been demonstrated to correlate with DNA fragmentation in this experimental paradigm.

10 Effect on cytokine release. An important function of monocytes/macrophages is their regulatory activity on other cellular populations of the immune system through the release of cytokines after stimulation. An ELISA to measure cytokine release is performed as follows. Human monocytes are incubated at a density of  $5 \times 10^5$  cells/ml with increasing concentrations of agonists or antagonists of the invention and under the same conditions, but  
15 in the absence of agonists or antagonists. For IL-12 production, the cells are primed overnight with IFN (100 U/ml) in presence of agonist or antagonist of the invention. LPS (10 ng/ml) is then added. Conditioned media are collected after 24h and kept frozen until use. Measurement of TNF-alpha, IL-10, MCP-1 and IL-8 is then performed using a commercially available ELISA kit (e. g, R & D Systems (Minneapolis, MN)) and applying the standard  
20 protocols provided with the kit.

Oxidative burst. Purified monocytes are plated in 96-w plate at  $2 \times 10^5$  cell/well. Increasing concentrations of agonists or antagonists of the invention are added to the wells in a total volume of 0.2 ml culture medium (RPMI 1640 + 10% FCS, glutamine and antibiotics). After  
25 3 days incubation, the plates are centrifuged and the medium is removed from the wells. To the macrophage monolayers, 0.2 ml per well of phenol red solution (140 mM NaCl, 10 mM potassium phosphate buffer pH 7.0, 5.5 mM dextrose, 0.56 mM phenol red and 19 U/ml of HRPO) is added, together with the stimulant (200 nM PMA). The plates are incubated at 37°C for 2 hours and the reaction is stopped by adding 20  $\mu$ l 1N NaOH per well. The  
30 absorbance is read at 610 nm. To calculate the amount of  $H_2O_2$  produced by the macrophages, a standard curve of a  $H_2O_2$  solution of known molarity is performed for each experiment.

The studies described in this example tested activity of agonists or antagonists of the invention. However, one skilled in the art could easily modify the exemplified studies to test the activity of polynucleotides or polypeptides of the invention (e.g., gene therapy).

5

*Example 25: Biological Effects of Agonists or Antagonists of the Invention*

Astrocyte and Neuronal Assays.

Agonists or antagonists of the invention, expressed in *Escherichia coli* and purified  
10 as described above, can be tested for activity in promoting the survival, neurite outgrowth, or  
phenotypic differentiation of cortical neuronal cells and for inducing the proliferation of glial  
fibrillary acidic protein immunopositive cells, astrocytes. The selection of cortical cells for  
the bioassay is based on the prevalent expression of FGF-1 and FGF-2 in cortical structures  
and on the previously reported enhancement of cortical neuronal survival resulting from  
15 FGF-2 treatment. A thymidine incorporation assay, for example, can be used to elucidate an  
agonist or antagonist of the invention's activity on these cells.

Moreover, previous reports describing the biological effects of FGF-2 (basic FGF) on  
cortical or hippocampal neurons *in vitro* have demonstrated increases in both neuron survival  
and neurite outgrowth (Walicke et al., "Fibroblast growth factor promotes survival of  
20 dissociated hippocampal neurons and enhances neurite extension." *Proc. Natl. Acad. Sci.*  
*USA* 83:3012-3016. (1986), assay herein incorporated by reference in its entirety). However,  
reports from experiments done on PC-12 cells suggest that these two responses are not  
necessarily synonymous and may depend on not only which FGF is being tested but also on  
which receptor(s) are expressed on the target cells. Using the primary cortical neuronal  
25 culture paradigm, the ability of an agonist or antagonist of the invention to induce neurite  
outgrowth can be compared to the response achieved with FGF-2 using, for example, a  
thymidine incorporation assay.

Fibroblast and endothelial cell assays.

30 Human lung fibroblasts are obtained from Clonetics (San Diego, CA) and maintained  
in growth media from Clonetics. Dermal microvascular endothelial cells are obtained from

Cell Applications (San Diego, CA). For proliferation assays, the human lung fibroblasts and dermal microvascular endothelial cells can be cultured at 5,000 cells/well in a 96-well plate for one day in growth medium. The cells are then incubated for one day in 0.1% BSA basal medium. After replacing the medium with fresh 0.1% BSA medium, the cells are incubated with the test proteins for 3 days. Alamar Blue (Alamar Biosciences, Sacramento, CA) is added to each well to a final concentration of 10%. The cells are incubated for 4 hr. Cell viability is measured by reading in a CytoFluor fluorescence reader. For the PGE<sub>2</sub> assays, the human lung fibroblasts are cultured at 5,000 cells/well in a 96-well plate for one day. After a medium change to 0.1% BSA basal medium, the cells are incubated with FGF-2 or agonists or antagonists of the invention with or without IL-1 $\alpha$  for 24 hours. The supernatants are collected and assayed for PGE<sub>2</sub> by EIA kit (Cayman, Ann Arbor, MI). For the IL-6 assays, the human lung fibroblasts are cultured at 5,000 cells/well in a 96-well plate for one day. After a medium change to 0.1% BSA basal medium, the cells are incubated with FGF-2 or with or without agonists or antagonists of the invention IL-1 $\alpha$  for 24 hours. The supernatants are collected and assayed for IL-6 by ELISA kit (Endogen, Cambridge, MA).

Human lung fibroblasts are cultured with FGF-2 or agonists or antagonists of the invention for 3 days in basal medium before the addition of Alamar Blue to assess effects on growth of the fibroblasts. FGF-2 should show a stimulation at 10 - 2500 ng/ml which can be used to compare stimulation with agonists or antagonists of the invention.

20

#### Parkinson Models.

The loss of motor function in Parkinson's disease is attributed to a deficiency of striatal dopamine resulting from the degeneration of the nigrostriatal dopaminergic projection neurons. An animal model for Parkinson's that has been extensively characterized involves the systemic administration of 1-methyl-4 phenyl 1,2,3,6-tetrahydropyridine (MPTP). In the CNS, MPTP is taken-up by astrocytes and catabolized by monoamine oxidase B to 1-methyl-4-phenyl pyridine (MPP<sup>+</sup>) and released. Subsequently, MPP<sup>+</sup> is actively accumulated in dopaminergic neurons by the high-affinity reuptake transporter for dopamine. MPP<sup>+</sup> is then concentrated in mitochondria by the electrochemical gradient and selectively inhibits nicotinamide adenine disphosphate: ubiquinone oxidoreductionase (complex I), thereby interfering with electron transport and eventually generating oxygen radicals.

30

It has been demonstrated in tissue culture paradigms that FGF-2 (basic FGF) has trophic activity towards nigral dopaminergic neurons (Ferrari et al., Dev. Biol. 1989). Recently, Dr. Unsicker's group has demonstrated that administering FGF-2 in gel foam implants in the striatum results in the near complete protection of nigral dopaminergic neurons from the toxicity associated with MPTP exposure (Otto and Unsicker, J. Neuroscience, 1990).

Based on the data with FGF-2, agonists or antagonists of the invention can be evaluated to determine whether it has an action similar to that of FGF-2 in enhancing dopaminergic neuronal survival *in vitro* and it can also be tested *in vivo* for protection of dopaminergic neurons in the striatum from the damage associated with MPTP treatment. The potential effect of an agonist or antagonist of the invention is first examined *in vitro* in a dopaminergic neuronal cell culture paradigm. The cultures are prepared by dissecting the midbrain floor plate from gestation day 14 Wistar rat embryos. The tissue is dissociated with trypsin and seeded at a density of 200,000 cells/cm<sup>2</sup> on polyorthinine-laminin coated glass coverslips. The cells are maintained in Dulbecco's Modified Eagle's medium and F12 medium containing hormonal supplements (N1). The cultures are fixed with paraformaldehyde after 8 days *in vitro* and are processed for tyrosine hydroxylase, a specific marker for dopaminergic neurons, immunohistochemical staining. Dissociated cell cultures are prepared from embryonic rats. The culture medium is changed every third day and the factors are also added at that time.

Since the dopaminergic neurons are isolated from animals at gestation day 14, a developmental time which is past the stage when the dopaminergic precursor cells are proliferating, an increase in the number of tyrosine hydroxylase immunopositive neurons would represent an increase in the number of dopaminergic neurons surviving *in vitro*. Therefore, if an agonist or antagonist of the invention acts to prolong the survival of dopaminergic neurons, it would suggest that the agonist or antagonist may be involved in Parkinson's Disease.

The studies described in this example tested activity of agonists or antagonists of the invention. However, one skilled in the art could easily modify the exemplified studies to test the activity of polynucleotides or polypeptides of the invention (e.g., gene therapy).

*Example 26: The Effect of Agonists or Antagonists of the Invention on the Growth of Vascular Endothelial Cells*

On day 1, human umbilical vein endothelial cells (HUVEC) are seeded at  $2.5 \times 10^4$  cells/35 mm dish density in M199 medium containing 4% fetal bovine serum (FBS), 16 units/ml heparin, and 50 units/ml endothelial cell growth supplements (ECGS, Biotechnology, Inc.). On day 2, the medium is replaced with M199 containing 10% FBS, 8 units/ml heparin. An agonist or antagonist of the invention, and positive controls, such as VEGF and basic FGF (bFGF) are added, at varying concentrations. On days 4 and 6, the medium is replaced. On day 8, cell number is determined with a Coulter Counter.

An increase in the number of HUVEC cells indicates that the compound of the invention may proliferate vascular endothelial cells, while a decrease in the number of HUVEC cell indicates that the compound of the invention inhibits vascular endothelial cells.

The studies described in this example tested activity of a polypeptide of the invention. However, one skilled in the art could easily modify the exemplified studies to test the activity of polynucleotides (e.g., gene therapy), agonists, and/or antagonists of the invention.

*Example 27: Rat Corneal Wound Healing Model*

This animal model shows the effect of an agonist or antagonist of the invention on neovascularization. The experimental protocol includes:

- a) Making a 1-1.5 mm long incision from the center of cornea into the stromal layer.
- b) Inserting a spatula below the lip of the incision facing the outer corner of the eye.
- c) Making a pocket (its base is 1-1.5 mm from the edge of the eye).
- d) Positioning a pellet, containing 50ng- 5ug of an agonist or antagonist of the invention, within the pocket.
- e) Treatment with an agonist or antagonist of the invention can also be applied topically to the corneal wounds in a dosage range of 20mg - 500mg (daily treatment for five days).

The studies described in this example tested activity of agonists or antagonists of the

invention. However, one skilled in the art could easily modify the exemplified studies to test the activity of polynucleotides or polypeptides of the invention (e.g., gene therapy).

*Example 28: Diabetic Mouse and Glucocorticoid-Impaired Wound Healing Models*

5

*A. Diabetic db+/db+ Mouse Model.*

To demonstrate that an agonist or antagonist of the invention accelerates the healing process, the genetically diabetic mouse model of wound healing is used. The full thickness wound healing model in the db+/db+ mouse is a well characterized, clinically relevant and  
10 reproducible model of impaired wound healing. Healing of the diabetic wound is dependent on formation of granulation tissue and re-epithelialization rather than contraction (Gartner, M.H. *et al.*, *J. Surg. Res.* 52:389 (1992); Greenhalgh, D.G. *et al.*, *Am. J. Pathol.* 136:1235 (1990)).

The diabetic animals have many of the characteristic features observed in Type II  
15 diabetes mellitus. Homozygous (db+/db+) mice are obese in comparison to their normal heterozygous (db+/+m) littermates. Mutant diabetic (db+/db+) mice have a single autosomal recessive mutation on chromosome 4 (db+) (Coleman *et al.* *Proc. Natl. Acad. Sci. USA* 77:283-293 (1982)). Animals show polyphagia, polydipsia and polyuria. Mutant diabetic mice (db+/db+) have elevated blood glucose, increased or normal insulin levels, and  
20 suppressed cell-mediated immunity (Mandel *et al.*, *J. Immunol.* 120:1375 (1978); Debray-Sachs, M. *et al.*, *Clin. Exp. Immunol.* 51(1):1-7 (1983); Leiter *et al.*, *Am. J. of Pathol.* 114:46-55 (1985)). Peripheral neuropathy, myocardial complications, and microvascular lesions, basement membrane thickening and glomerular filtration abnormalities have been described in these animals (Norido, F. *et al.*, *Exp. Neurol.* 83(2):221-232 (1984); Robertson *et al.*,  
25 *Diabetes* 29(1):60-67 (1980); Giacomelli *et al.*, *Lab Invest.* 40(4):460-473 (1979); Coleman, D.L., *Diabetes* 31 (Suppl):1-6 (1982)). These homozygous diabetic mice develop hyperglycemia that is resistant to insulin analogous to human type II diabetes (Mandel *et al.*, *J. Immunol.* 120:1375-1377 (1978)).

The characteristics observed in these animals suggests that healing in this model may  
30 be similar to the healing observed in human diabetes (Greenhalgh, *et al.*, *Am. J. of Pathol.* 136:1235-1246 (1990)).

Genetically diabetic female C57BL/KsJ (db+/db+) mice and their non-diabetic



(db+/+m) heterozygous littermates are used in this study (Jackson Laboratories). The animals are purchased at 6 weeks of age and are 8 weeks old at the beginning of the study. Animals are individually housed and received food and water ad libitum. All manipulations are performed using aseptic techniques. The experiments are conducted according to the  
5 rules and guidelines of Human Genome Sciences, Inc. Institutional Animal Care and Use Committee and the Guidelines for the Care and Use of Laboratory Animals.

Wounding protocol is performed according to previously reported methods (Tsuboi, R. and Rifkin, D.B., *J. Exp. Med.* 172:245-251 (1990)). Briefly, on the day of wounding, animals are anesthetized with an intraperitoneal injection of Avertin (0.01 mg/mL), 2,2,2-  
10 tribromoethanol and 2-methyl-2-butanol dissolved in deionized water. The dorsal region of the animal is shaved and the skin washed with 70% ethanol solution and iodine. The surgical area is dried with sterile gauze prior to wounding. An 8 mm full-thickness wound is then created using a Keyes tissue punch. Immediately following wounding, the surrounding skin is gently stretched to eliminate wound expansion. The wounds are left open for the duration  
15 of the experiment. Application of the treatment is given topically for 5 consecutive days commencing on the day of wounding. Prior to treatment, wounds are gently cleansed with sterile saline and gauze sponges.

Wounds are visually examined and photographed at a fixed distance at the day of surgery and at two day intervals thereafter. Wound closure is determined by daily  
20 measurement on days 1-5 and on day 8. Wounds are measured horizontally and vertically using a calibrated Jameson caliper. Wounds are considered healed if granulation tissue is no longer visible and the wound is covered by a continuous epithelium.

An agonist or antagonist of the invention is administered using at a range different doses, from 4mg to 500mg per wound per day for 8 days in vehicle. Vehicle control groups  
25 received 50mL of vehicle solution.

Animals are euthanized on day 8 with an intraperitoneal injection of sodium pentobarbital (300mg/kg). The wounds and surrounding skin are then harvested for histology and immunohistochemistry. Tissue specimens are placed in 10% neutral buffered formalin in tissue cassettes between biopsy sponges for further processing.

30 Three groups of 10 animals each (5 diabetic and 5 non-diabetic controls) are evaluated: 1) Vehicle placebo control, 2) untreated group, and 3) treated group.

Wound closure is analyzed by measuring the area in the vertical and horizontal axis and

obtaining the total square area of the wound. Contraction is then estimated by establishing the differences between the initial wound area (day 0) and that of post treatment (day 8). The wound area on day 1 is 64mm<sup>2</sup>, the corresponding size of the dermal punch. Calculations are made using the following formula:

5

$$[\text{Open area on day 8}] - [\text{Open area on day 1}] / [\text{Open area on day 1}]$$

Specimens are fixed in 10% buffered formalin and paraffin embedded blocks are sectioned perpendicular to the wound surface (5mm) and cut using a Reichert-Jung microtome.

10 Routine hematoxylin-eosin (H&E) staining is performed on cross-sections of bisected wounds. Histologic examination of the wounds are used to assess whether the healing process and the morphologic appearance of the repaired skin is altered by treatment with an agonist or antagonist of the invention. This assessment included verification of the presence of cell accumulation, inflammatory cells, capillaries, fibroblasts, re-epithelialization and  
15 epidermal maturity (Greenhalgh, D.G. *et al.*, *Am. J. Pathol.* 136:1235 (1990)). A calibrated lens micrometer is used by a blinded observer.

Tissue sections are also stained immunohistochemically with a polyclonal rabbit anti-human keratin antibody using ABC Elite detection system. Human skin is used as a positive tissue control while non-immune IgG is used as a negative control. Keratinocyte growth is  
20 determined by evaluating the extent of reepithelialization of the wound using a calibrated lens micrometer.

Proliferating cell nuclear antigen/cyclin (PCNA) in skin specimens is demonstrated by using anti-PCNA antibody (1:50) with an ABC Elite detection system. Human colon cancer served as a positive tissue control and human brain tissue is used as a negative tissue  
25 control. Each specimen included a section with omission of the primary antibody and substitution with non-immune mouse IgG. Ranking of these sections is based on the extent of proliferation on a scale of 0-8, the lower side of the scale reflecting slight proliferation to the higher side reflecting intense proliferation.

Experimental data are analyzed using an unpaired t test. A p value of < 0.05 is  
30 considered significant.

### *B. Steroid Impaired Rat Model*

The inhibition of wound healing by steroids has been well documented in various *in vitro* and *in vivo* systems (Wahl, Glucocorticoids and Wound healing. In: Anti-Inflammatory Steroid Action: Basic and Clinical Aspects. 280-302 (1989); Wahl *et al.*, *J. Immunol.* 115: 476-481 (1975); Werb *et al.*, *J. Exp. Med.* 147:1684-1694 (1978)). Glucocorticoids retard wound healing by inhibiting angiogenesis, decreasing vascular permeability (Ebert *et al.*, *An. Intern. Med.* 37:701-705 (1952)), fibroblast proliferation, and collagen synthesis (Beck *et al.*, *Growth Factors.* 5: 295-304 (1991); Haynes *et al.*, *J. Clin. Invest.* 61: 703-797 (1978)) and producing a transient reduction of circulating monocytes (Haynes *et al.*, *J. Clin. Invest.* 61: 703-797 (1978); Wahl, "Glucocorticoids and wound healing", In: Antiinflammatory Steroid Action: Basic and Clinical Aspects, Academic Press, New York, pp. 280-302 (1989)). The systemic administration of steroids to impaired wound healing is a well establish phenomenon in rats (Beck *et al.*, *Growth Factors.* 5: 295-304 (1991); Haynes *et al.*, *J. Clin. Invest.* 61: 703-797 (1978); Wahl, "Glucocorticoids and wound healing", In: Antiinflammatory Steroid Action: Basic and Clinical Aspects, Academic Press, New York, pp. 280-302 (1989); Pierce *et al.*, *Proc. Natl. Acad. Sci. USA* 86: 2229-2233 (1989)).

To demonstrate that an agonist or antagonist of the invention can accelerate the healing process, the effects of multiple topical applications of the agonist or antagonist on full thickness excisional skin wounds in rats in which healing has been impaired by the systemic administration of methylprednisolone is assessed.

Young adult male Sprague Dawley rats weighing 250-300 g (Charles River Laboratories) are used in this example. The animals are purchased at 8 weeks of age and are 9 weeks old at the beginning of the study. The healing response of rats is impaired by the systemic administration of methylprednisolone (17mg/kg/rat intramuscularly) at the time of wounding. Animals are individually housed and received food and water *ad libitum*. All manipulations are performed using aseptic techniques. This study is conducted according to the rules and guidelines of Human Genome Sciences, Inc. Institutional Animal Care and Use Committee and the Guidelines for the Care and Use of Laboratory Animals.

The wounding protocol is followed according to section A, above. On the day of wounding, animals are anesthetized with an intramuscular injection of ketamine (50 mg/kg) and xylazine (5 mg/kg). The dorsal region of the animal is shaved and the skin washed with 70% ethanol and iodine solutions. The surgical area is dried with sterile gauze prior to wounding. An 8 mm full-thickness wound is created using a Keyes tissue punch. The

wounds are left open for the duration of the experiment. Applications of the testing materials are given topically once a day for 7 consecutive days commencing on the day of wounding and subsequent to methylprednisolone administration. Prior to treatment, wounds are gently cleansed with sterile saline and gauze sponges.

5           Wounds are visually examined and photographed at a fixed distance at the day of wounding and at the end of treatment. Wound closure is determined by daily measurement on days 1-5 and on day 8. Wounds are measured horizontally and vertically using a calibrated Jameson caliper. Wounds are considered healed if granulation tissue is no longer visible and the wound is covered by a continuous epithelium.

10           The agonist or antagonist of the invention is administered using at a range different doses, from 4mg to 500mg per wound per day for 8 days in vehicle. Vehicle control groups received 50mL of vehicle solution.

          Animals are euthanized on day 8 with an intraperitoneal injection of sodium pentobarbital (300mg/kg). The wounds and surrounding skin are then harvested for  
15 histology. Tissue specimens are placed in 10% neutral buffered formalin in tissue cassettes between biopsy sponges for further processing.

          Four groups of 10 animals each (5 with methylprednisolone and 5 without glucocorticoid) are evaluated: 1) Untreated group 2) Vehicle placebo control 3) treated groups.

20           Wound closure is analyzed by measuring the area in the vertical and horizontal axis and obtaining the total area of the wound. Closure is then estimated by establishing the differences between the initial wound area (day 0) and that of post treatment (day 8). The wound area on day 1 is 64mm<sup>2</sup>, the corresponding size of the dermal punch. Calculations are made using the following formula:

25

$$[\text{Open area on day 8}] - [\text{Open area on day 1}] / [\text{Open area on day 1}]$$

Specimens are fixed in 10% buffered formalin and paraffin embedded blocks are sectioned perpendicular to the wound surface (5mm) and cut using an Olympus microtome. Routine  
30 hematoxylin-eosin (H&E) staining is performed on cross-sections of bisected wounds. Histologic examination of the wounds allows assessment of whether the healing process and the morphologic appearance of the repaired skin is improved by treatment with an agonist or

antagonist of the invention. A calibrated lens micrometer is used by a blinded observer to determine the distance of the wound gap.

Experimental data are analyzed using an unpaired t test. A p value of  $< 0.05$  is considered significant.

- 5       The studies described in this example tested activity of agonists or antagonists of the invention. However, one skilled in the art could easily modify the exemplified studies to test the activity of polynucleotides or polypeptides of the invention (e.g., gene therapy).

*Example 29: Lymphadema Animal Model*

10

The purpose of this experimental approach is to create an appropriate and consistent lymphedema model for testing the therapeutic effects of an agonist or antagonist of the invention in lymphangiogenesis and re-establishment of the lymphatic circulatory system in the rat hind limb. Effectiveness is measured by swelling volume of the affected limb, quantification of the amount of lymphatic vasculature, total blood plasma protein, and histopathology. Acute lymphedema is observed for 7-10 days. Perhaps more importantly, the chronic progress of the edema is followed for up to 3-4 weeks.

Prior to beginning surgery, blood sample is drawn for protein concentration analysis. Male rats weighing approximately ~350g are dosed with Pentobarbital. Subsequently, the right legs are shaved from knee to hip. The shaved area is swabbed with gauze soaked in 70% EtOH. Blood is drawn for serum total protein testing. Circumference and volumetric measurements are made prior to injecting dye into paws after marking 2 measurement levels (0.5 cm above heel, at mid-pt of dorsal paw). The intradermal dorsum of both right and left paws are injected with 0.05 ml of 1% Evan's Blue. Circumference and volumetric measurements are then made following injection of dye into paws.

Using the knee joint as a landmark, a mid-leg inguinal incision is made circumferentially allowing the femoral vessels to be located. Forceps and hemostats are used to dissect and separate the skin flaps. After locating the femoral vessels, the lymphatic vessel that runs along side and underneath the vessel(s) is located. The main lymphatic vessels in this area are then electrically coagulated or suture ligated.

Using a microscope, muscles in back of the leg (near the semitendinosus and adductors) are bluntly dissected. The popliteal lymph node is then located. The 2 proximal

and 2 distal lymphatic vessels and distal blood supply of the popliteal node are then and ligated by suturing. The popliteal lymph node, and any accompanying adipose tissue, is then removed by cutting connective tissues.

Care is taken to control any mild bleeding resulting from this procedure. After  
5 lymphatics are occluded, the skin flaps are sealed by using liquid skin (Vetbond) (AJ Buck). The separated skin edges are sealed to the underlying muscle tissue while leaving a gap of ~0.5 cm around the leg. Skin also may be anchored by suturing to underlying muscle when necessary.

To avoid infection, animals are housed individually with mesh (no bedding).  
10 Recovering animals are checked daily through the optimal edematous peak, which typically occurred by day 5-7. The plateau edematous peak are then observed. To evaluate the intensity of the lymphedema, the circumference and volumes of 2 designated places on each paw before operation and daily for 7 days are measured. The effect plasma proteins on lymphedema is determined and whether protein analysis is a useful testing perimeter is also  
15 investigated. The weights of both control and edematous limbs are evaluated at 2 places. Analysis is performed in a blind manner.

Circumference Measurements: Under brief gas anesthetic to prevent limb movement, a cloth tape is used to measure limb circumference. Measurements are done at the ankle bone and dorsal paw by 2 different people then those 2 readings are averaged. Readings are  
20 taken from both control and edematous limbs.

Volumetric Measurements: On the day of surgery, animals are anesthetized with Pentobarbital and are tested prior to surgery. For daily volumetrics animals are under brief halothane anesthetic (rapid immobilization and quick recovery), both legs are shaved and equally marked using waterproof marker on legs. Legs are first dipped in water, then dipped  
25 into instrument to each marked level then measured by Buxco edema software(Chen/Victor). Data is recorded by one person, while the other is dipping the limb to marked area.

Blood-plasma protein measurements: Blood is drawn, spun, and serum separated prior to surgery and then at conclusion for total protein and Ca<sup>2+</sup> comparison.

Limb Weight Comparison: After drawing blood, the animal is prepared for tissue  
30 collection. The limbs are amputated using a quillitine, then both experimental and control legs are cut at the ligature and weighed. A second weighing is done as the tibio-cacaneal joint is disarticulated and the foot is weighed.

Histological Preparations: The transverse muscle located behind the knee (popliteal) area is dissected and arranged in a metal mold, filled with freezeGel, dipped into cold methylbutane, placed into labeled sample bags at - 80EC until sectioning. Upon sectioning, the muscle is observed under fluorescent microscopy for lymphatics..

- 5 The studies described in this example tested activity of agonists or antagonists of the invention. However, one skilled in the art could easily modify the exemplified studies to test the activity of polynucleotides or polypeptides of the invention (e.g., gene therapy).

10 *Example 30: Suppression of TNF alpha-induced adhesion molecule expression by a Agonist or Antagonist of the Invention*

- 15 The recruitment of lymphocytes to areas of inflammation and angiogenesis involves specific receptor-ligand interactions between cell surface adhesion molecules (CAMs) on lymphocytes and the vascular endothelium. The adhesion process, in both normal and pathological settings, follows a multi-step cascade that involves intercellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1), and endothelial leukocyte adhesion molecule-1 (E-selectin) expression on endothelial cells (EC). The expression of these molecules and others on the vascular endothelium determines the efficiency with which leukocytes may adhere to the local vasculature and extravasate into the local tissue during the development of an inflammatory response. The local concentration of cytokines and growth factor participate in the modulation of the expression of these CAMs.

Tumor necrosis factor alpha (TNF-a), a potent proinflammatory cytokine, is a stimulator of all three CAMs on endothelial cells and may be involved in a wide variety of inflammatory responses, often resulting in a pathological outcome.

- 25 The potential of an agonist or antagonist of the invention to mediate a suppression of TNF-a induced CAM expression can be examined. A modified ELISA assay which uses ECs as a solid phase absorbent is employed to measure the amount of CAM expression on TNF-a treated ECs when co-stimulated with a member of the FGF family of proteins.

- 30 To perform the experiment, human umbilical vein endothelial cell (HUVEC) cultures are obtained from pooled cord harvests and maintained in growth medium (EGM-2; Clonetics, San Diego, CA) supplemented with 10% FCS and 1% penicillin/streptomycin in a 37 degree C humidified incubator containing 5% CO<sub>2</sub>. HUVECs are seeded in 96-well

plates at concentrations of  $1 \times 10^4$  cells/well in EGM medium at 37 degree C for 18-24 hrs or until confluent. The monolayers are subsequently washed 3 times with a serum-free solution of RPMI-1640 supplemented with 100 U/ml penicillin and 100 mg/ml streptomycin, and treated with a given cytokine and/or growth factor(s) for 24 h at 37 degree C. Following  
5 incubation, the cells are then evaluated for CAM expression.

Human Umbilical Vein Endothelial cells (HUVECs) are grown in a standard 96 well plate to confluence. Growth medium is removed from the cells and replaced with 90 ul of 199 Medium (10% FBS). Samples for testing and positive or negative controls are added to the plate in triplicate (in 10 ul volumes). Plates are incubated at 37 degree C for either 5 h  
10 (selectin and integrin expression) or 24 h (integrin expression only). Plates are aspirated to remove medium and 100  $\mu$ l of 0.1% paraformaldehyde-PBS(with  $\text{Ca}^{++}$  and  $\text{Mg}^{++}$ ) is added to each well. Plates are held at 4°C for 30 min.

Fixative is then removed from the wells and wells are washed 1X with PBS(+Ca,Mg)+0.5% BSA and drained. Do not allow the wells to dry. Add 10  $\mu$ l of diluted  
15 primary antibody to the test and control wells. Anti-ICAM-1-Biotin, Anti-VCAM-1-Biotin and Anti-E-selectin-Biotin are used at a concentration of 10  $\mu$ g/ml (1:10 dilution of 0.1 mg/ml stock antibody). Cells are incubated at 37°C for 30 min. in a humidified environment. Wells are washed X3 with PBS(+Ca,Mg)+0.5% BSA.

Then add 20  $\mu$ l of diluted ExtrAvidin-Alkaline Phosphatase (1:5,000 dilution) to each  
20 well and incubated at 37°C for 30 min. Wells are washed X3 with PBS(+Ca,Mg)+0.5% BSA. 1 tablet of p-Nitrophenol Phosphate pNPP is dissolved in 5 ml of glycine buffer (pH 10.4). 100  $\mu$ l of pNPP substrate in glycine buffer is added to each test well. Standard wells in triplicate are prepared from the working dilution of the ExtrAvidin-Alkaline Phosphatase in glycine buffer:  $1:5,000 (10^0) > 10^{-0.5} > 10^{-1} > 10^{-1.5}$ . 5  $\mu$ l of each dilution is added to triplicate  
25 wells and the resulting AP content in each well is 5.50 ng, 1.74 ng, 0.55 ng, 0.18 ng. 100  $\mu$ l of pNPP reagent must then be added to each of the standard wells. The plate must be incubated at 37°C for 4h. A volume of 50  $\mu$ l of 3M NaOH is added to all wells. The results are quantified on a plate reader at 405 nm. The background subtraction option is used on blank wells filled with glycine buffer only. The template is set up to indicate the  
30 concentration of AP-conjugate in each standard well [ 5.50 ng; 1.74 ng; 0.55 ng; 0.18 ng]. Results are indicated as amount of bound AP-conjugate in each sample.

The studies described in this example tested activity of agonists or antagonists of the



invention. However, one skilled in the art could easily modify the exemplified studies to test the activity of polynucleotides or polypeptides of the invention (e.g., gene therapy).

*Example 31: Production Of Polypeptide of the Invention For High-Throughput Screening Assays*

The following protocol produces a supernatant containing polypeptide of the present invention to be tested. This supernatant can then be used in the Screening Assays described in Examples 33-42.

10 First, dilute Poly-D-Lysine (644 587 Boehringer-Mannheim) stock solution (1mg/ml in PBS) 1:20 in PBS (w/o calcium or magnesium 17-516F Biowhittaker) for a working solution of 50ug/ml. Add 200 ul of this solution to each well (24 well plates) and incubate at RT for 20 minutes. Be sure to distribute the solution over each well (note: a 12-channel pipetter may be used with tips on every other channel). Aspirate off the Poly-D-Lysine  
15 solution and rinse with 1ml PBS (Phosphate Buffered Saline). The PBS should remain in the well until just prior to plating the cells and plates may be poly-lysine coated in advance for up to two weeks.

Plate 293T cells (do not carry cells past P+20) at  $2 \times 10^5$  cells/well in .5ml DMEM(Dulbecco's Modified Eagle Medium)(with 4.5 G/L glucose and L-glutamine (12-  
20 604F Biowhittaker))/10% heat inactivated FBS(14-503F Biowhittaker)/1x Penstrep(17-602E Biowhittaker). Let the cells grow overnight.

The next day, mix together in a sterile solution basin: 300 ul Lipofectamine (18324-012 Gibco/BRL) and 5ml Optimem I (31985070 Gibco/BRL)/96-well plate. With a small volume multi-channel pipetter, aliquot approximately 2ug of an expression vector containing  
25 a polynucleotide insert, produced by the methods described in Examples 8-10, into an appropriately labeled 96-well round bottom plate. With a multi-channel pipetter, add 50ul of the Lipofectamine/Optimem I mixture to each well. Pipette up and down gently to mix. Incubate at RT 15-45 minutes. After about 20 minutes, use a multi-channel pipetter to add 150ul Optimem I to each well. As a control, one plate of vector DNA lacking an insert  
30 should be transfected with each set of transfections.

Preferably, the transfection should be performed by tag-teaming the following tasks. By tag-teaming, hands on time is cut in half, and the cells do not spend too much time on

PBS. First, person A aspirates off the media from four 24-well plates of cells, and then person B rinses each well with .5-1ml PBS. Person A then aspirates off PBS rinse, and person B, using a 12-channel pipetter with tips on every other channel, adds the 200ul of DNA/Lipofectamine/Optimem 1 complex to the odd wells first, then to the even wells, to  
 5 each row on the 24-well plates. Incubate at 37 degree C for 6 hours.

While cells are incubating, prepare appropriate media, either 1%BSA in DMEM with 1x penstrep, or HGS CHO-5 media (116.6 mg/L of CaCl<sub>2</sub> (anhyd); 0.00130 mg/L CuSO<sub>4</sub>-5H<sub>2</sub>O; 0.050 mg/L of Fe(NO<sub>3</sub>)<sub>3</sub>-9H<sub>2</sub>O; 0.417 mg/L of FeSO<sub>4</sub>-7H<sub>2</sub>O; 311.80 mg/L of KCl; 28.64 mg/L of MgCl<sub>2</sub>; 48.84 mg/L of MgSO<sub>4</sub>; 6995.50 mg/L of NaCl; 2400.0 mg/L of  
 10 NaHCO<sub>3</sub>; 62.50 mg/L of NaH<sub>2</sub>PO<sub>4</sub>-H<sub>2</sub>O; 71.02 mg/L of Na<sub>2</sub>HPO<sub>4</sub>; .4320 mg/L of ZnSO<sub>4</sub>-7H<sub>2</sub>O; .002 mg/L of Arachidonic Acid ; 1.022 mg/L of Cholesterol; .070 mg/L of DL-alpha-Tocopherol-Acetate; 0.0520 mg/L of Linoleic Acid; 0.010 mg/L of Linolenic Acid; 0.010 mg/L of Myristic Acid; 0.010 mg/L of Oleic Acid; 0.010 mg/L of Palmitic Acid; 0.010 mg/L of Palmitic Acid; 100 mg/L of Pluronic F-68; 0.010 mg/L of Stearic Acid; 2.20 mg/L of  
 15 Tween 80; 4551 mg/L of D-Glucose; 130.85 mg/ml of L- Alanine; 147.50 mg/ml of L- Arginine-HCL; 7.50 mg/ml of L-Asparagine-H<sub>2</sub>O; 6.65 mg/ml of L-Aspartic Acid; 29.56 mg/ml of L-Cystine-2HCL-H<sub>2</sub>O; 31.29 mg/ml of L-Cystine-2HCL; 7.35 mg/ml of L- Glutamic Acid; 365.0 mg/ml of L-Glutamine; 18.75 mg/ml of Glycine; 52.48 mg/ml of L- Histidine-HCL-H<sub>2</sub>O; 106.97 mg/ml of L-Isoleucine; 111.45 mg/ml of L-Leucine; 163.75  
 20 mg/ml of L-Lysine HCL; 32.34 mg/ml of L-Methionine; 68.48 mg/ml of L-Phenylalanine; 40.0 mg/ml of L-Proline; 26.25 mg/ml of L-Serine; 101.05 mg/ml of L-Threonine; 19.22 mg/ml of L-Tryptophan; 91.79 mg/ml of L-Tyrosine-2Na-2H<sub>2</sub>O; and 99.65 mg/ml of L- Valine; 0.0035 mg/L of Biotin; 3.24 mg/L of D-Ca Pantothenate; 11.78 mg/L of Choline Chloride; 4.65 mg/L of Folic Acid; 15.60 mg/L of i-Inositol; 3.02 mg/L of Niacinamide; 3.00  
 25 mg/L of Pyridoxal HCL; 0.031 mg/L of Pyridoxine HCL; 0.319 mg/L of Riboflavin; 3.17 mg/L of Thiamine HCL; 0.365 mg/L of Thymidine; 0.680 mg/L of Vitamin B<sub>12</sub>; 25 mM of HEPES Buffer; 2.39 mg/L of Na Hypoxanthine; 0.105 mg/L of Lipoic Acid; 0.081 mg/L of Sodium Putrescine-2HCL; 55.0 mg/L of Sodium Pyruvate; 0.0067 mg/L of Sodium Selenite; 20uM of Ethanolamine; 0.122 mg/L of Ferric Citrate; 41.70 mg/L of Methyl-B-Cyclodextrin  
 30 complexed with Linoleic Acid; 33.33 mg/L of Methyl-B-Cyclodextrin complexed with Oleic Acid; 10 mg/L of Methyl-B-Cyclodextrin complexed with Retinal Acetate. Adjust

osmolarity to 327 mOsm) with 2mm glutamine and 1x penstrep. (BSA (81-068-3 Bayer) 100gm dissolved in 1L DMEM for a 10% BSA stock solution). Filter the media and collect 50 ul for endotoxin assay in 15ml polystyrene conical.

5 The transfection reaction is terminated, preferably by tag-teaming, at the end of the incubation period. Person A aspirates off the transfection media, while person B adds 1.5ml appropriate media to each well. Incubate at 37 degree C for 45 or 72 hours depending on the media used: 1%BSA for 45 hours or CHO-5 for 72 hours.

10 On day four, using a 300ul multichannel pipetter, aliquot 600ul in one 1ml deep well plate and the remaining supernatant into a 2ml deep well. The supernatants from each well can then be used in the assays described in Examples 33-40.

It is specifically understood that when activity is obtained in any of the assays described below using a supernatant, the activity originates from either the polypeptide of the present invention directly (e.g., as a secreted protein) or by polypeptide of the present invention inducing expression of other proteins, which are then secreted into the supernatant.  
15 Thus, the invention further provides a method of identifying the protein in the supernatant characterized by an activity in a particular assay.

*Example 32: Construction of GAS Reporter Construct*

20 One signal transduction pathway involved in the differentiation and proliferation of cells is called the Jaks-STATs pathway. Activated proteins in the Jaks-STATs pathway bind to gamma activation site "GAS" elements or interferon-sensitive responsive element ("ISRE"), located in the promoter of many genes. The binding of a protein to these elements alter the expression of the associated gene.

25 GAS and ISRE elements are recognized by a class of transcription factors called Signal Transducers and Activators of Transcription, or "STATs." There are six members of the STATs family. Stat1 and Stat3 are present in many cell types, as is Stat2 (as response to IFN-alpha is widespread). Stat4 is more restricted and is not in many cell types though it has been found in T helper class 1, cells after treatment with IL-12. Stat5 was originally called  
30 mammary growth factor, but has been found at higher concentrations in other cells including myeloid cells. It can be activated in tissue culture cells by many cytokines.

The STATs are activated to translocate from the cytoplasm to the nucleus upon

tyrosine phosphorylation by a set of kinases known as the Janus Kinase ("Jaks") family. Jaks represent a distinct family of soluble tyrosine kinases and include Tyk2, Jak1, Jak2, and Jak3. These kinases display significant sequence similarity and are generally catalytically inactive in resting cells.

5       The Jaks are activated by a wide range of receptors summarized in the Table below. (Adapted from review by Schidler and Darnell, Ann. Rev. Biochem. 64:621-51 (1995).) A cytokine receptor family, capable of activating Jaks, is divided into two groups: (a) Class 1 includes receptors for IL-2, IL-3, IL-4, IL-6, IL-7, IL-9, IL-11, IL-12, IL-15, Epo, PRL, GH, G-CSF, GM-CSF, LIF, CNTF, and thrombopoietin; and (b) Class 2 includes IFN-a, IFN-g,  
10   and IL-10. The Class 1 receptors share a conserved cysteine motif (a set of four conserved cysteines and one tryptophan) and a WSXWS motif (a membrane proximal region encoding Trp-Ser-Xxx-Trp-Ser (SEQ ID NO:1686)).

      Thus, on binding of a ligand to a receptor, Jaks are activated, which in turn activate STATs, which then translocate and bind to GAS elements. This entire process is  
15   encompassed in the Jaks-STATs signal transduction pathway.

      Therefore, activation of the Jaks-STATs pathway, reflected by the binding of the GAS or the ISRE element, can be used to indicate proteins involved in the proliferation and differentiation of cells. For example, growth factors and cytokines are known to activate the Jaks-STATs pathway. (See Table below.) Thus, by using GAS elements linked to reporter  
20   molecules, activators of the Jaks-STATs pathway can be identified.

	<u>Ligand</u>	<u>tyk2</u>	<u>JAKs</u>			<u>STATs</u>	<u>GAS(elements) or ISRE</u>
			<u>Jak1</u>	<u>Jak2</u>	<u>Jak3</u>		
	<u>IFN family</u>						
5	IFN-a/B	+	+	-	-	1,2,3	ISRE
	IFN-g (IRF1>Lys6>IFP)		+	+	-	1	GAS
	IL-10	+	?	?	-	1,3	
10	<u>gp130 family</u>						
	IL-6 (Pleiotrohic) (IRF1>Lys6>IFP)	+	+	+	?	1,3	GAS
	IL-11(Pleiotrohic)	?	+	?	?	1,3	
	OnM(Pleiotrohic)	?	+	+	?	1,3	
15	LIF(Pleiotrohic)	?	+	+	?	1,3	
	CNTF(Pleiotrohic)	-/+	+	+	?	1,3	
	G-CSF(Pleiotrohic)	?	+	?	?	1,3	
	IL-12(Pleiotrohic)	+	-	+	+	1,3	
20	<u>g-C family</u>						
	IL-2 (lymphocytes)	-	+	-	+	1,3,5	GAS
	IL-4 (lymph/myeloid) >>Ly6(IgH)	-	+	-	+	6	GAS (IRF1 = IFP
	IL-7 (lymphocytes)	-	+	-	+	5	GAS
25	IL-9 (lymphocytes)	-	+	-	+	5	GAS
	IL-13 (lymphocyte)	-	+	?	?	6	GAS
	IL-15	?	+	?	+	5	GAS
	<u>gp140 family</u>						
30	IL-3 (myeloid) (IRF1>IFP>>Ly6)	-	-	+	-	5	GAS
	IL-5 (myeloid)	-	-	+	-	5	GAS
	GM-CSF (myeloid)	-	-	+	-	5	GAS

GH	?	-	+	-	5
PRL	?	+/-	+	-	1,3,5
EPO	?	-	+	-	5
CAS>IRF1=IFP>>Ly6)					

5

GAS(B-

EGF	?	+	+	-	1,3	GAS (IRF1)
-----	---	---	---	---	-----	------------

10

PDGF	?	+	+	-	1,3	GAS (not IRF1)
CSF-1	?	+	+	-	1,3	

To construct a synthetic GAS containing promoter element, which is used in the Biological Assays described in Examples 33-34, a PCR based strategy is employed to generate a GAS-SV40 promoter sequence. The 5' primer contains four tandem copies of the GAS binding site found in the IRF1 promoter and previously demonstrated to bind STATs upon induction with a range of cytokines (Rothman et al., Immunity 1:457-468 (1994).), although other GAS or ISRE elements can be used instead. The 5' primer also contains 18bp of sequence complementary to the SV40 early promoter sequence and is flanked with an XhoI site. The sequence of the 5' primer is:

10 5':GCGCCTCGAGATTTCCCCGAAATCTAGATTTCCCCGAAATGATTTCCCC  
GAAATGATTTCCCCGAAATATCTGCCATCTCAATTAG:3' (SEQ ID NO:1687)

The downstream primer is complementary to the SV40 promoter and is flanked with a Hind III site: 5':GCGGCAAGCTTTTTGCAAAGCCTAGGC:3' (SEQ ID NO:1688)

15 PCR amplification is performed using the SV40 promoter template present in the B-gal:promoter plasmid obtained from Clontech. The resulting PCR fragment is digested with XhoI/Hind III and subcloned into BLSK2-. (Stratagene.) Sequencing with forward and reverse primers confirms that the insert contains the following sequence:

20 5':CTCGAGATTTCCCCGAAATCTAGATTTCCCCGAAATGATTTCCCCGAAA  
TGATTTCCCCGAAATATCTGCCATCTCAATTAGTCAGCAACCATAGTCCCG  
CCCCTAACTCCGCCCATCCCGCCCCTAACTCCGCCCAGTTCCGCCCATTCT  
CCGCCCCATGGCTGACTAATTTTTTTTATTTATGCAGAGGCCGAGGCCGCC  
TCGGCCTCTGAGCTATTCCAGAAGTAGTGAGGAGGCTTTTTTGGAGGCCTA  
25 GGCTTTTGCAAAAAAGCTT:3' (SEQ ID NO:1689)

With this GAS promoter element linked to the SV40 promoter, a GAS:SEAP2 reporter construct is next engineered. Here, the reporter molecule is a secreted alkaline phosphatase, or "SEAP." Clearly, however, any reporter molecule can be instead of SEAP, in this or in any of the other Examples. Well known reporter  
30 molecules that can be used instead of SEAP include chloramphenicol

acetyltransferase (CAT), luciferase, alkaline phosphatase, B-galactosidase, green fluorescent protein (GFP), or any protein detectable by an antibody.

The above sequence confirmed synthetic GAS-SV40 promoter element is subcloned into the pSEAP-Promoter vector obtained from Clontech using HindIII and  
5 XhoI, effectively replacing the SV40 promoter with the amplified GAS:SV40 promoter element, to create the GAS-SEAP vector. However, this vector does not contain a neomycin resistance gene, and therefore, is not preferred for mammalian expression systems.

Thus, in order to generate mammalian stable cell lines expressing the GAS-  
10 SEAP reporter, the GAS-SEAP cassette is removed from the GAS-SEAP vector using Sall and NotI, and inserted into a backbone vector containing the neomycin resistance gene, such as pGFP-1 (Clontech), using these restriction sites in the multiple cloning site, to create the GAS-SEAP/Neo vector. Once this vector is transfected into mammalian cells, this vector can then be used as a reporter molecule for GAS binding  
15 as described in Examples 33-34.

Other constructs can be made using the above description and replacing GAS with a different promoter sequence. For example, construction of reporter molecules containing NFK-B and EGR promoter sequences are described in Examples 35 and 36. However, many other promoters can be substituted using the protocols described  
20 in these Examples. For instance, SRE, IL-2, NFAT, or Osteocalcin promoters can be substituted, alone or in combination (e.g., GAS/NF-KB/EGR, GAS/NF-KB, IL-2/NFAT, or NF-KB/GAS). Similarly, other cell lines can be used to test reporter construct activity, such as HELA (epithelial), HUVEC (endothelial), Reh (B-cell), Saos-2 (osteoblast), HUVAC (aortic), or Cardiomyocyte.

25

*Example 33: High-Throughput Screening Assay for T-cell Activity.*

The following protocol is used to assess T-cell activity by identifying factors, and determining whether supernate containing a polypeptide of the invention  
30 proliferates and/or differentiates T-cells. T-cell activity is assessed using the



GAS/SEAP/Neo construct produced in Example 32. Thus, factors that increase SEAP activity indicate the ability to activate the Jaks-STATS signal transduction pathway. The T-cell used in this assay is Jurkat T-cells (ATCC Accession No. TIB-152), although Molt-3 cells (ATCC Accession No. CRL-1552) and Molt-4 cells (ATCC  
5 Accession No. CRL-1582) cells can also be used.

Jurkat T-cells are lymphoblastic CD4+ Th1 helper cells. In order to generate stable cell lines, approximately 2 million Jurkat cells are transfected with the GAS-SEAP/neo vector using DMRIE-C (Life Technologies)(transfection procedure described below). The transfected cells are seeded to a density of approximately  
10 20,000 cells per well and transfectants resistant to 1 mg/ml gentamicin selected. Resistant colonies are expanded and then tested for their response to increasing concentrations of interferon gamma. The dose response of a selected clone is demonstrated.

Specifically, the following protocol will yield sufficient cells for 75 wells  
15 containing 200 ul of cells. Thus, it is either scaled up, or performed in multiple to generate sufficient cells for multiple 96 well plates. Jurkat cells are maintained in RPMI + 10% serum with 1%Pen-Strep. Combine 2.5 mls of OPTI-MEM (Life Technologies) with 10 ug of plasmid DNA in a T25 flask. Add 2.5 ml OPTI-MEM containing 50 ul of DMRIE-C and incubate at room temperature for 15-45 mins.

20 During the incubation period, count cell concentration, spin down the required number of cells ( $10^7$  per transfection), and resuspend in OPTI-MEM to a final concentration of  $10^7$  cells/ml. Then add 1ml of  $1 \times 10^7$  cells in OPTI-MEM to T25 flask and incubate at 37 degree C for 6 hrs. After the incubation, add 10 ml of RPMI + 15% serum.

25 The Jurkat:GAS-SEAP stable reporter lines are maintained in RPMI + 10% serum, 1 mg/ml Gentamicin, and 1% Pen-Strep. These cells are treated with supernatants containing polypeptide of the present invention or polypeptide of the present invention induced polypeptides as produced by the protocol described in Example 31.

30 On the day of treatment with the supernatant, the cells should be washed and

resuspended in fresh RPMI + 10% serum to a density of 500,000 cells per ml. The exact number of cells required will depend on the number of supernatants being screened. For one 96 well plate, approximately 10 million cells (for 10 plates, 100 million cells) are required.

5           Transfer the cells to a triangular reservoir boat, in order to dispense the cells into a 96 well dish, using a 12 channel pipette. Using a 12 channel pipette, transfer 200 ul of cells into each well (therefore adding 100, 000 cells per well).

          After all the plates have been seeded, 50 ul of the supernatants are transferred directly from the 96 well plate containing the supernatants into each well using a 12  
10   channel pipette. In addition, a dose of exogenous interferon gamma (0.1, 1.0, 10 ng) is added to wells H9, H10, and H11 to serve as additional positive controls for the assay.

          The 96 well dishes containing Jurkat cells treated with supernatants are placed in an incubator for 48 hrs (note: this time is variable between 48-72 hrs). 35 ul  
15   samples from each well are then transferred to an opaque 96 well plate using a 12 channel pipette. The opaque plates should be covered (using sellophene covers) and stored at -20 degree C until SEAP assays are performed according to Example 37. The plates containing the remaining treated cells are placed at 4 degree C and serve as a source of material for repeating the assay on a specific well if desired.

20           As a positive control, 100 Unit/ml interferon gamma can be used which is known to activate Jurkat T cells. Over 30 fold induction is typically observed in the positive control wells.

          The above protocol may be used in the generation of both transient, as well as, stable transfected cells, which would be apparent to those of skill in the art.

25

*Example 34: High-Throughput Screening Assay Identifying Myeloid Activity*

          The following protocol is used to assess myeloid activity of polypeptide of the present invention by determining whether polypeptide of the present invention  
30   proliferates and/or differentiates myeloid cells. Myeloid cell activity is assessed using

the GAS/SEAP/Neo construct produced in Example 32. Thus, factors that increase SEAP activity indicate the ability to activate the Jaks-STATS signal transduction pathway. The myeloid cell used in this assay is U937, a pre-monocyte cell line, although TF-1, HL60, or KG1 can be used.

- 5        To transiently transfect U937 cells with the GAS/SEAP/Neo construct produced in Example 32, a DEAE-Dextran method (Kharbanda et. al., 1994, Cell Growth & Differentiation, 5:259-265) is used. First, harvest  $2 \times 10^7$  U937 cells and wash with PBS. The U937 cells are usually grown in RPMI 1640 medium containing 10% heat-inactivated fetal bovine serum (FBS) supplemented with 100 units/ml  
10       penicillin and 100 mg/ml streptomycin.

Next, suspend the cells in 1 ml of 20 mM Tris-HCl (pH 7.4) buffer containing 0.5 mg/ml DEAE-Dextran, 8 ug GAS-SEAP2 plasmid DNA, 140 mM NaCl, 5 mM KCl, 375 uM  $\text{Na}_2\text{HPO}_4 \cdot 7\text{H}_2\text{O}$ , 1 mM  $\text{MgCl}_2$ , and 675 uM  $\text{CaCl}_2$ . Incubate at 37 degrees C for 45 min.

- 15       Wash the cells with RPMI 1640 medium containing 10% FBS and then resuspend in 10 ml complete medium and incubate at 37 degree C for 36 hr.

The GAS-SEAP/U937 stable cells are obtained by growing the cells in 400 ug/ml G418. The G418-free medium is used for routine growth but every one to two months, the cells should be re-grown in 400 ug/ml G418 for couple of passages.

- 20       These cells are tested by harvesting  $1 \times 10^8$  cells (this is enough for ten 96-well plates assay) and wash with PBS. Suspend the cells in 200 ml above described growth medium, with a final density of  $5 \times 10^5$  cells/ml. Plate 200 ul cells per well in the 96-well plate (or  $1 \times 10^5$  cells/well).

- 25       Add 50 ul of the supernatant prepared by the protocol described in Example 31. Incubate at 37 degree C for 48 to 72 hr. As a positive control, 100 Unit/ml interferon gamma can be used which is known to activate U937 cells. Over 30 fold induction is typically observed in the positive control wells. SEAP assay the supernatant according to the protocol described in Example 37.

- 30       *Example 35: High-Throughput Screening Assay Identifying Neuronal Activity.*

When cells undergo differentiation and proliferation, a group of genes are activated through many different signal transduction pathways. One of these genes, EGR1 (early growth response gene 1), is induced in various tissues and cell types upon activation. The promoter of EGR1 is responsible for such induction. Using the EGR1 promoter linked to reporter molecules, activation of cells can be assessed by polypeptide of the present invention.

Particularly, the following protocol is used to assess neuronal activity in PC12 cell lines. PC12 cells (rat phenochromocytoma cells) are known to proliferate and/or differentiate by activation with a number of mitogens, such as TPA (tetradecanoyl phorbol acetate), NGF (nerve growth factor), and EGF (epidermal growth factor). The EGR1 gene expression is activated during this treatment. Thus, by stably transfecting PC12 cells with a construct containing an EGR promoter linked to SEAP reporter, activation of PC12 cells by polypeptide of the present invention can be assessed.

The EGR/SEAP reporter construct can be assembled by the following protocol. The EGR-1 promoter sequence (-633 to +1)(Sakamoto K et al., Oncogene 6:867-871 (1991)) can be PCR amplified from human genomic DNA using the following primers:

5' GCGCTCGAGGGATGACAGCGATAGAACCCCGG -3' (SEQ ID NO: 1690)

5' GCGAAGCTTCGCGACTCCCGGATCCGCCTC-3' (SEQ ID NO: 1691)

Using the GAS:SEAP/Neo vector produced in Example 32, EGR1 amplified product can then be inserted into this vector. Linearize the GAS:SEAP/Neo vector using restriction enzymes XhoI/HindIII, removing the GAS/SV40 stuffer. Restrict the EGR1 amplified product with these same enzymes. Ligate the vector and the EGR1 promoter.

To prepare 96 well-plates for cell culture, two mls of a coating solution (1:30 dilution of collagen type I (Upstate Biotech Inc. Cat#08-115) in 30% ethanol (filter

sterilized)) is added per one 10 cm plate or 50 ml per well of the 96-well plate, and allowed to air dry for 2 hr.

PC12 cells are routinely grown in RPMI-1640 medium (Bio Whittaker) containing 10% horse serum (JRH BIOSCIENCES, Cat. # 12449-78P), 5% heat-inactivated fetal bovine serum (FBS) supplemented with 100 units/ml penicillin and 100 ug/ml streptomycin on a precoated 10 cm tissue culture dish. One to four split is done every three to four days. Cells are removed from the plates by scraping and resuspended with pipetting up and down for more than 15 times.

Transfect the EGR/SEAP/Neo construct into PC12 using the Lipofectamine protocol described in Example 31. EGR-SEAP/PC12 stable cells are obtained by growing the cells in 300 ug/ml G418. The G418-free medium is used for routine growth but every one to two months, the cells should be re-grown in 300 ug/ml G418 for couple of passages.

To assay for neuronal activity, a 10 cm plate with cells around 70 to 80% confluent is screened by removing the old medium. Wash the cells once with PBS (Phosphate buffered saline). Then starve the cells in low serum medium (RPMI-1640 containing 1% horse serum and 0.5% FBS with antibiotics) overnight.

The next morning, remove the medium and wash the cells with PBS. Scrape off the cells from the plate, suspend the cells well in 2 ml low serum medium. Count the cell number and add more low serum medium to reach final cell density as  $5 \times 10^5$  cells/ml.

Add 200 ul of the cell suspension to each well of 96-well plate (equivalent to  $1 \times 10^5$  cells/well). Add 50 ul supernatant produced by Example 31, 37 degree C for 48 to 72 hr. As a positive control, a growth factor known to activate PC12 cells through EGR can be used, such as 50 ng/ul of Neuronal Growth Factor (NGF). Over fifty-fold induction of SEAP is typically seen in the positive control wells. SEAP assay the supernatant according to Example 37.

#### *Example 36: High-Throughput Screening Assay for T-cell Activity*

NF-KB (Nuclear Factor KB) is a transcription factor activated by a wide variety of agents including the inflammatory cytokines IL-1 and TNF, CD30 and CD40, lymphotoxin-alpha and lymphotoxin-beta, by exposure to LPS or thrombin, and by expression of certain viral gene products. As a transcription factor, NF-KB  
5 regulates the expression of genes involved in immune cell activation, control of apoptosis (NF- KB appears to shield cells from apoptosis), B and T-cell development, anti-viral and antimicrobial responses, and multiple stress responses.

In non-stimulated conditions, NF- KB is retained in the cytoplasm with I-KB (Inhibitor KB). However, upon stimulation, I- KB is phosphorylated and degraded,  
10 causing NF- KB to shuttle to the nucleus, thereby activating transcription of target genes. Target genes activated by NF- KB include IL-2, IL-6, GM-CSF, ICAM-1 and class I MHC.

Due to its central role and ability to respond to a range of stimuli, reporter constructs utilizing the NF-KB promoter element are used to screen the supernatants  
15 produced in Example 31. Activators or inhibitors of NF-KB would be useful in treating, preventing, and/or diagnosing diseases. For example, inhibitors of NF-KB could be used to treat those diseases related to the acute or chronic activation of NF-KB, such as rheumatoid arthritis.

To construct a vector containing the NF-KB promoter element, a PCR based  
20 strategy is employed. The upstream primer contains four tandem copies of the NF-KB binding site (GGGGACTTTCCC) (SEQ ID NO:1692), 18 bp of sequence complementary to the 5' end of the SV40 early promoter sequence, and is flanked with an XhoI site:

5':GCGGCCTCGAGGGGACTTTCCCGGGGACTTTCCGGGGACTTTCCGGGAC  
25 TTTCCATCCTGCCATCTCAATTAG:3' (SEQ ID NO:1693)

The downstream primer is complementary to the 3' end of the SV40 promoter and is flanked with a Hind III site:

5':GCGGCAAGCTTTTGGCAAAGCCTAGGC:3' (SEQ ID NO:1688)

PCR amplification is performed using the SV40 promoter template present in  
30 the pB-gal:promoter plasmid obtained from Clontech. The resulting PCR fragment is

digested with XhoI and Hind III and subcloned into BLSK2-. (Stratagene)  
Sequencing with the T7 and T3 primers confirms the insert contains the following  
sequence:

5':CTCGAGGGGACTTTCCCGGGGACTTTCCGGGGACTTTCCGGGACTTTCC  
5 ATCTGCCATCTCAATTAGTCAGCAACCATAGTCCCGCCCCTAACTCCGCCC  
ATCCCGCCCCTAACTCCGCCCAGTTCCGCCCATTCTCCGCCCCATGGCTGA  
CTAATTTTTTTTATTTATGCAGAGGCCGAGGCCGCCTCGGCCTCTGAGCTA  
TTCCAGAAAGTAGTGAGGAGGCTTTTTTGGAGGCCTAGGCTTTTGCAAAAA  
GCTT:3' (SEQ ID NO:1694)

10       Next, replace the SV40 minimal promoter element present in the pSEAP2-  
promoter plasmid (Clontech) with this NF-KB/SV40 fragment using XhoI and  
HindIII. However, this vector does not contain a neomycin resistance gene, and  
therefore, is not preferred for mammalian expression systems.

15       In order to generate stable mammalian cell lines, the NF-KB/SV40/SEAP  
cassette is removed from the above NF-KB/SEAP vector using restriction enzymes  
Sall and NotI, and inserted into a vector containing neomycin resistance. Particularly,  
the NF-KB/SV40/SEAP cassette was inserted into pGFP-1 (Clontech), replacing the  
GFP gene, after restricting pGFP-1 with Sall and NotI.

20       Once NF-KB/SV40/SEAP/Neo vector is created, stable Jurkat T-cells are  
created and maintained according to the protocol described in Example 33. Similarly,  
the method for assaying supernatants with these stable Jurkat T-cells is also described  
in Example 33. As a positive control, exogenous TNF alpha (0.1, 1, 10 ng) is added to  
wells H9, H10, and H11, with a 5-10 fold activation typically observed.

#### 25   *Example 37: Assay for SEAP Activity*

As a reporter molecule for the assays described in Examples 33-36, SEAP  
activity is assayed using the Tropix Phospho-light Kit (Cat. BP-400) according to the  
following general procedure. The Tropix Phospho-light Kit supplies the Dilution,  
30   Assay, and Reaction Buffers used below.

Prime a dispenser with the 2.5x Dilution Buffer and dispense 15 ul of 2.5x dilution buffer into Optiplates containing 35 ul of a supernatant. Seal the plates with a plastic sealer and incubate at 65 degree C for 30 min. Separate the Optiplates to avoid uneven heating.

- 5 Cool the samples to room temperature for 15 minutes. Empty the dispenser and prime with the Assay Buffer. Add 50 ml Assay Buffer and incubate at room temperature 5 min. Empty the dispenser and prime with the Reaction Buffer (see the table below).. Add 50 ul Reaction Buffer and incubate at room temperature for 20 minutes. Since the intensity of the chemiluminescent signal is time dependent, and it
- 10 takes about 10 minutes to read 5 plates on luminometer, one should treat 5 plates at each time and start the second set 10 minutes later.

Read the relative light unit in the luminometer. Set H12 as blank, and print the results. An increase in chemiluminescence indicates reporter activity.

15 Reaction Buffer Formulation:

# of plates	Rxn buffer diluent (ml)	CSPD (ml)
10	60	3
11	65	3.25
12	70	3.5
13	75	3.75
14	80	4
15	85	4.25
16	90	4.5
17	95	4.75
18	100	5
19	105	5.25
20	110	5.5
21	115	5.75
22	120	6



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23	125	6.25
24	130	6.5
25	135	6.75
26	140	7
27	145	7.25
28	150	7.5
29	155	7.75
30	160	8
31	165	8.25
32	170	8.5
33	175	8.75
34	180	9
35	185	9.25
36	190	9.5
37	195	9.75
38	200	10
39	205	10.25
40	210	10.5
41	215	10.75
42	220	11
43	225	11.25
44	230	11.5
45	235	11.75
46	240	12
47	245	12.25
48	250	12.5
49	255	12.75
50	260	13

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*Example 38: High-Throughput Screening Assay Identifying Changes in Small*

*Molecule Concentration and Membrane Permeability*

Binding of a ligand to a receptor is known to alter intracellular levels of small molecules, such as calcium, potassium, sodium, and pH, as well as alter membrane potential. These alterations can be measured in an assay to identify supernatants which bind to receptors of a particular cell. Although the following protocol describes an assay for calcium, this protocol can easily be modified to detect changes in potassium, sodium, pH, membrane potential, or any other small molecule which is detectable by a fluorescent probe.

10 The following assay uses Fluorometric Imaging Plate Reader ("FLIPR") to measure changes in fluorescent molecules (Molecular Probes) that bind small molecules. Clearly, any fluorescent molecule detecting a small molecule can be used instead of the calcium fluorescent molecule, fluo-4 (Molecular Probes, Inc.; catalog no. F-14202), used here.

15 For adherent cells, seed the cells at 10,000 -20,000 cells/well in a Co-star black 96-well plate with clear bottom. The plate is incubated in a CO<sub>2</sub> incubator for 20 hours. The adherent cells are washed two times in Biotek washer with 200 ul of HBSS (Hank's Balanced Salt Solution) leaving 100 ul of buffer after the final wash.

A stock solution of 1 mg/ml fluo-4 is made in 10% pluronic acid DMSO. To load the cells with fluo-4, 50 ul of 12 ug/ml fluo-4 is added to each well. The plate is incubated at 37 degrees C in a CO<sub>2</sub> incubator for 60 min. The plate is washed four times in the Biotek washer with HBSS leaving 100 ul of buffer.

For non-adherent cells, the cells are spun down from culture media. Cells are re-suspended to  $2-5 \times 10^6$  cells/ml with HBSS in a 50-ml conical tube. 4 ul of 1 mg/ml fluo-4 solution in 10% pluronic acid DMSO is added to each ml of cell suspension. The tube is then placed in a 37 degrees C water bath for 30-60 min. The cells are washed twice with HBSS, resuspended to  $1 \times 10^6$  cells/ml, and dispensed into a microplate. 100 ul/well. The plate is centrifuged at 1000 rpm for 5 min. The plate is then washed once in Denley Cell Wash with 200 ul, followed by an aspiration step to 100 ul final volume.

For a non-cell based assay, each well contains a fluorescent molecule, such as fluo-4 . The supernatant is added to the well, and a change in fluorescence is detected.

To measure the fluorescence of intracellular calcium, the FLIPR is set for the following parameters: (1) System gain is 300-800 mW; (2) Exposure time is 0.4 second; (3) Camera F/stop is F/2; (4) Excitation is 488 nm; (5) Emission is 530 nm; and (6) Sample addition is 50 ul. Increased emission at 530 nm indicates an extracellular signaling event caused by the a molecule, either polypeptide of the present invention or a molecule induced by polypeptide of the present invention, which has resulted in an increase in the intracellular  $Ca^{++}$  concentration.

*Example 40: High-Throughput Screening Assay Identifying Tyrosine Kinase Activity*

The Protein Tyrosine Kinases (PTK) represent a diverse group of transmembrane and cytoplasmic kinases. Within the Receptor Protein Tyrosine Kinase (RPTK) group are receptors for a range of mitogenic and metabolic growth factors including the PDGF, FGF, EGF, NGF, HGF and Insulin receptor subfamilies. In addition there are a large family of RPTKs for which the corresponding ligand is unknown. Ligands for RPTKs include mainly secreted small proteins, but also membrane-bound and extracellular matrix proteins.

Activation of RPTK by ligands involves ligand-mediated receptor dimerization, resulting in transphosphorylation of the receptor subunits and activation of the cytoplasmic tyrosine kinases. The cytoplasmic tyrosine kinases include receptor associated tyrosine kinases of the src-family (e.g., src, yes, lck, lyn, fyn) and non-receptor linked and cytosolic protein tyrosine kinases, such as the Jak family, members of which mediate signal transduction triggered by the cytokine superfamily of receptors (e.g., the Interleukins, Interferons, GM-CSF, and Leptin).

Because of the wide range of known factors capable of stimulating tyrosine kinase activity, identifying whether polypeptide of the present invention or a molecule induced by polypeptide of the present invention is capable of activating tyrosine

kinase signal transduction pathways is of interest. Therefore, the following protocol is designed to identify such molecules capable of activating the tyrosine kinase signal transduction pathways.

Seed target cells (e.g., primary keratinocytes) at a density of approximately  
5 25,000 cells per well in a 96 well Loprodyne Silent Screen Plates purchased from Nalge Nunc (Naperville, IL). The plates are sterilized with two 30 minute rinses with 100% ethanol, rinsed with water and dried overnight. Some plates are coated for 2 hr with 100 ml of cell culture grade type I collagen (50 mg/ml), gelatin (2%) or polylysine (50 mg/ml), all of which can be purchased from Sigma Chemicals (St.  
10 Louis, MO) or 10% Matrigel purchased from Becton Dickinson (Bedford, MA), or calf serum, rinsed with PBS and stored at 4 degree C. Cell growth on these plates is assayed by seeding 5,000 cells/well in growth medium and indirect quantitation of cell number through use of alamarBlue as described by the manufacturer Alamar Biosciences, Inc. (Sacramento, CA) after 48 hr. Falcon plate covers #3071 from  
15 Becton Dickinson (Bedford, MA) are used to cover the Loprodyne Silent Screen Plates. Falcon Microtest III cell culture plates can also be used in some proliferation experiments.

To prepare extracts, A431 cells are seeded onto the nylon membranes of Loprodyne plates (20,000/200ml/well) and cultured overnight in complete medium.  
20 Cells are quiesced by incubation in serum-free basal medium for 24 hr. After 5-20 minutes treatment with EGF (60ng/ml) or 50 ul of the supernatant produced in Example 31, the medium was removed and 100 ml of extraction buffer ((20 mM HEPES pH 7.5, 0.15 M NaCl, 1% Triton X-100, 0.1% SDS, 2 mM Na<sub>3</sub>VO<sub>4</sub>, 2 mM Na<sub>4</sub>P<sub>2</sub>O<sub>7</sub> and a cocktail of protease inhibitors (# 1836170) obtained from  
25 Boehringer Mannheim (Indianapolis, IN) is added to each well and the plate is shaken on a rotating shaker for 5 minutes at 4°C. The plate is then placed in a vacuum transfer manifold and the extract filtered through the 0.45 mm membrane bottoms of each well using house vacuum. Extracts are collected in a 96-well catch/assay plate in the bottom of the vacuum manifold and immediately placed on  
30 ice. To obtain extracts clarified by centrifugation, the content of each well, after

detergent solubilization for 5 minutes, is removed and centrifuged for 15 minutes at 4 degree C at 16,000 x g.

Test the filtered extracts for levels of tyrosine kinase activity. Although many methods of detecting tyrosine kinase activity are known, one method is described  
5 here.

Generally, the tyrosine kinase activity of a supernatant is evaluated by determining its ability to phosphorylate a tyrosine residue on a specific substrate (a biotinylated peptide). Biotinylated peptides that can be used for this purpose include PSK1 (corresponding to amino acids 6-20 of the cell division kinase cdc2-p34) and  
10 PSK2 (corresponding to amino acids 1-17 of gastrin). Both peptides are substrates for a range of tyrosine kinases and are available from Boehringer Mannheim.

The tyrosine kinase reaction is set up by adding the following components in order. First, add 10ul of 5uM Biotinylated Peptide, then 10ul ATP/Mg<sub>2</sub><sup>+</sup> (5mM ATP/50mM MgCl<sub>2</sub>), then 10ul of 5x Assay Buffer (40mM imidazole hydrochloride,  
15 pH7.3, 40 mM beta-glycerophosphate, 1mM EGTA, 100mM MgCl<sub>2</sub>, 5 mM MnCl<sub>2</sub>, 0.5 mg/ml BSA), then 5ul of Sodium Vanadate(1mM), and then 5ul of water. Mix the components gently and preincubate the reaction mix at 30 degree C for 2 min. Initial the reaction by adding 10ul of the control enzyme or the filtered supernatant.

The tyrosine kinase assay reaction is then terminated by adding 10 ul of  
20 120mM EDTA and place the reactions on ice.

Tyrosine kinase activity is determined by transferring 50 ul aliquot of reaction mixture to a microtiter plate (MTP) module and incubating at 37 degree C for 20 min. This allows the streptavidin coated 96 well plate to associate with the biotinylated peptide. Wash the MTP module with 300ul/well of PBS four times. Next add 75 ul  
25 of anti-phosphotyrosine antibody conjugated to horse radish peroxidase(anti-P-Tyr-POD(0.5u/ml)) to each well and incubate at 37 degree C for one hour. Wash the well as above.

Next add 100ul of peroxidase substrate solution (Boehringer Mannheim) and incubate at room temperature for at least 5 mins (up to 30 min). Measure the  
30 absorbance of the sample at 405 nm by using ELISA reader. The level of bound

peroxidase activity is quantitated using an ELISA reader and reflects the level of tyrosine kinase activity.

*Example 41: High-Throughput Screening Assay Identifying Phosphorylation Activity*

5

As a potential alternative and/or compliment to the assay of protein tyrosine kinase activity described in Example 40, an assay which detects activation (phosphorylation) of major intracellular signal transduction intermediates can also be used. For example, as described below one particular assay can detect tyrosine phosphorylation of the Erk-1 and Erk-2 kinases. However, phosphorylation of other molecules, such as Raf, JNK, p38 MAP, Map kinase kinase (MEK), MEK kinase, Src, Muscle specific kinase (MuSK), IRAK, Tec, and Janus, as well as any other phosphoserine, phosphotyrosine, or phosphothreonine molecule, can be detected by substituting these molecules for Erk-1 or Erk-2 in the following assay.

15 Specifically, assay plates are made by coating the wells of a 96-well ELISA plate with 0.1ml of protein G (1ug/ml) for 2 hr at room temp, (RT). The plates are then rinsed with PBS and blocked with 3% BSA/PBS for 1 hr at RT. The protein G plates are then treated with 2 commercial monoclonal antibodies (100ng/well) against Erk-1 and Erk-2 (1 hr at RT) (Santa Cruz Biotechnology). (To detect other molecules, this step can easily be modified by substituting a monoclonal antibody detecting any of the above described molecules.) After 3-5 rinses with PBS, the plates are stored at 4 degree C until use.

25 A431 cells are seeded at 20,000/well in a 96-well Loprodyne filterplate and cultured overnight in growth medium. The cells are then starved for 48 hr in basal medium (DMEM) and then treated with EGF (6ng/well) or 50 ul of the supernatants obtained in Example 31 for 5-20 minutes. The cells are then solubilized and extracts filtered directly into the assay plate.

30 After incubation with the extract for 1 hr at RT, the wells are again rinsed. As a positive control, a commercial preparation of MAP kinase (10ng/well) is used in place of A431 extract. Plates are then treated with a commercial polyclonal (rabbit)

antibody (1ug/ml) which specifically recognizes the phosphorylated epitope of the Erk-1 and Erk-2 kinases (1 hr at RT). This antibody is biotinylated by standard procedures. The bound polyclonal antibody is then quantitated by successive incubations with Europium-streptavidin and Europium fluorescence enhancing reagent in the Wallac DELFIA instrument (time-resolved fluorescence). An increased fluorescent signal over background indicates a phosphorylation by polypeptide of the present invention or a molecule induced by polypeptide of the present invention.

*Example 42: Assay for the Stimulation of Bone Marrow CD34+ Cell Proliferation*

10

This assay is based on the ability of human CD34+ to proliferate in the presence of hematopoietic growth factors and evaluates the ability of isolated polypeptides expressed in mammalian cells to stimulate proliferation of CD34+ cells.

It has been previously shown that most mature precursors will respond to only a single signal. More immature precursors require at least two signals to respond. Therefore, to test the effect of polypeptides on hematopoietic activity of a wide range of progenitor cells, the assay contains a given polypeptide in the presence or absence of other hematopoietic growth factors. Isolated cells are cultured for 5 days in the presence of Stem Cell Factor (SCF) in combination with tested sample. SCF alone has a very limited effect on the proliferation of bone marrow (BM) cells, acting in such conditions only as a "survival" factor. However, combined with any factor exhibiting stimulatory effect on these cells (e.g., IL-3), SCF will cause a synergistic effect. Therefore, if the tested polypeptide has a stimulatory effect on a hematopoietic progenitors, such activity can be easily detected. Since normal BM cells have a low level of cycling cells, it is likely that any inhibitory effect of a given polypeptide, or agonists or antagonists thereof, might not be detected. Accordingly, assays for an inhibitory effect on progenitors is preferably tested in cells that are first subjected to *in vitro* stimulation with SCF+IL+3, and then contacted with the compound that is being evaluated for inhibition of such induced proliferation.

30 Briefly, CD34+ cells are isolated using methods known in the art. The cells

are thawed and resuspended in medium (QBSF 60 serum-free medium with 1% L-glutamine (500ml) Quality Biological, Inc., Gaithersburg, MD Cat# 160-204-101). After several gentle centrifugation steps at 200 x g, cells are allowed to rest for one hour. The cell count is adjusted to  $2.5 \times 10^5$  cells/ml. During this time, 100  $\mu$ l of  
5 sterile water is added to the peripheral wells of a 96-well plate. The cytokines that can be tested with a given polypeptide in this assay is rhSCF (R&D Systems, Minneapolis, MN, Cat# 255-SC) at 50 ng/ml alone and in combination with rhSCF and rhIL-3 (R&D Systems, Minneapolis, MN, Cat# 203-ML) at 30 ng/ml. After one hour, 10  $\mu$ l of prepared cytokines, 50  $\mu$ l of the supernatants prepared in Example 31  
10 (supernatants at 1:2 dilution = 50  $\mu$ l) and 20  $\mu$ l of diluted cells are added to the media which is already present in the wells to allow for a final total volume of 100  $\mu$ l. The plates are then placed in a 37°C/5% CO<sub>2</sub> incubator for five days.

Eighteen hours before the assay is harvested, 0.5  $\mu$ Ci/well of [3H] Thymidine is added in a 10  $\mu$ l volume to each well to determine the proliferation rate. The  
15 experiment is terminated by harvesting the cells from each 96-well plate to a filtermat using the Tomtec Harvester 96. After harvesting, the filtermats are dried, trimmed and placed into OmniFilter assemblies consisting of one OmniFilter plate and one OmniFilter Tray. 60  $\mu$ l Microscint is added to each well and the plate sealed with TopSeal-A press-on sealing film. A bar code 15 sticker is affixed to the first plate for  
20 counting. The sealed plates is then loaded and the level of radioactivity determined via the Packard Top Count and the printed data collected for analysis. The level of radioactivity reflects the amount of cell proliferation.

The studies described in this example test the activity of a given polypeptide to stimulate bone marrow CD34+ cell proliferation. One skilled in the art could  
25 easily modify the exemplified studies to test the activity of polynucleotides (e.g., gene therapy), antibodies, agonists, and/or antagonists and fragments and variants thereof. As a nonlimiting example, potential antagonists tested in this assay would be expected to inhibit cell proliferation in the presence of cytokines and/or to increase the inhibition of cell proliferation in the presence of cytokines and a given polypeptide.  
30 In contrast, potential agonists tested in this assay would be expected to enhance cell



proliferation and/or to decrease the inhibition of cell proliferation in the presence of cytokines and a given polypeptide.

The ability of a gene to stimulate the proliferation of bone marrow CD34+ cells indicates that polynucleotides and polypeptides corresponding to the gene are  
5 useful for the diagnosis and treatment of disorders affecting the immune system and hematopoiesis. Representative uses are described in the "Immune Activity" and "Infectious Disease" sections above, and elsewhere herein.

*Example 43: Assay for Extracellular Matrix Enhanced Cell Response (EMECCR)*

10

The objective of the Extracellular Matrix Enhanced Cell Response (EMECCR) assay is to identify gene products (e.g., isolated polypeptides) that act on the hematopoietic stem cells in the context of the extracellular matrix (ECM) induced signal.

15 Cells respond to the regulatory factors in the context of signal(s) received from the surrounding microenvironment. For example, fibroblasts, and endothelial and epithelial stem cells fail to replicate in the absence of signals from the ECM. Hematopoietic stem cells can undergo self-renewal in the bone marrow, but not in *in vitro* suspension culture. The ability of stem cells to undergo self-renewal *in vitro* is  
20 dependent upon their interaction with the stromal cells and the ECM protein fibronectin (fn). Adhesion of cells to fn is mediated by the  $\alpha_5\beta_1$  and  $\alpha_4\beta_1$  integrin receptors, which are expressed by human and mouse hematopoietic stem cells. The factor(s) which integrate with the ECM environment and responsible for stimulating stem cell self-renewal has not yet been identified. Discovery of such factors should  
25 be of great interest in gene therapy and bone marrow transplant applications

Briefly, polystyrene, non tissue culture treated, 96-well plates are coated with fn fragment at a coating concentration of  $0.2 \mu\text{g}/\text{cm}^2$ . Mouse bone marrow cells are plated (1,000 cells/well) in 0.2 ml of serum-free medium. Cells cultured in the presence of IL-3 (5 ng/ml) + SCF (50 ng/ml) would serve as the positive control,

conditions under which little self-renewal but pronounced differentiation of the stem cells is to be expected. Gene products of the invention (e.g., including, but not limited to, polynucleotides and polypeptides of the present invention, and supernatants produced in Example 31), are tested with appropriate negative controls in the presence and absence of SCF(5.0 ng/ml), where test factor supernates represent 10% of the total assay volume. The plated cells are then allowed to grow by incubating in a low oxygen environment ( 5% CO<sub>2</sub>, 7% O<sub>2</sub>, and 88% N<sub>2</sub> ) tissue culture incubator for 7 days. The number of proliferating cells within the wells is then quantitated by measuring thymidine incorporation into cellular DNA. Verification of the positive hits in the assay will require phenotypic characterization of the cells, which can be accomplished by scaling up of the culture system and using appropriate antibody reagents against cell surface antigens and FACScan.

One skilled in the art could easily modify the exemplified studies to test the activity of polynucleotides (e.g., gene therapy), antibodies, agonists, and/or antagonists and fragments and variants thereof.

If a particular polypeptide of the present invention is found to be a stimulator of hematopoietic progenitors, polynucleotides and polypeptides corresponding to the gene encoding said polypeptide may be useful for the diagnosis and treatment of disorders affecting the immune system and hematopoiesis. Representative uses are described in the "Immune Activity" and "Infectious Disease" sections above, and elsewhere herein. The gene product may also be useful in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types.

Additionally, the polynucleotides and/or polypeptides of the gene of interest and/or agonists and/or antagonists thereof, may also be employed to inhibit the proliferation and differentiation of hematopoietic cells and therefore may be employed to protect bone marrow stem cells from chemotherapeutic agents during chemotherapy. This antiproliferative effect may allow administration of higher doses of chemotherapeutic agents and, therefore, more effective chemotherapeutic treatment.

Moreover, polynucleotides and polypeptides corresponding to the gene of interest may also be useful for the treatment and diagnosis of hematopoietic related disorders such as, for example, anemia, pancytopenia, leukopenia, thrombocytopenia or leukemia since stromal cells are important in the production of cells of hematopoietic lineages. The uses include bone marrow cell ex-vivo culture, bone marrow transplantation, bone marrow reconstitution, radiotherapy or chemotherapy of neoplasia.

*Example 44: Human Dermal Fibroblast and Aortic Smooth Muscle Cell Proliferation*

10

The polypeptide of interest is added to cultures of normal human dermal fibroblasts (NHDF) and human aortic smooth muscle cells (AoSMC) and two co-assays are performed with each sample. The first assay examines the effect of the polypeptide of interest on the proliferation of normal human dermal fibroblasts (NHDF) or aortic smooth muscle cells (AoSMC). Aberrant growth of fibroblasts or smooth muscle cells is a part of several pathological processes, including fibrosis, and restenosis. The second assay examines IL6 production by both NHDF and SMC. IL6 production is an indication of functional activation. Activated cells will have increased production of a number of cytokines and other factors, which can result in a proinflammatory or immunomodulatory outcome. Assays are run with and without co-TNF $\alpha$  stimulation, in order to check for costimulatory or inhibitory activity.

Briefly, on day 1, 96-well black plates are set up with 1000 cells/well (NHDF) or 2000 cells/well (AoSMC) in 100  $\mu$ l culture media. NHDF culture media contains: Clonetics FB basal media, 1mg/ml hFGF, 5mg/ml insulin, 50mg/ml gentamycin, 2%FBS, while AoSMC culture media contains Clonetics SM basal media, 0.5  $\mu$ g/ml hEGF, 5mg/ml insulin, 1 $\mu$ g/ml hFGF, 50mg/ml gentamycin, 50  $\mu$ g/ml Amphotericin B, 5%FBS. After incubation at 37°C for at least 4-5 hours, culture media is aspirated and replaced with growth arrest media. Growth arrest media for NHDF contains fibroblast basal media, 50mg/ml gentamycin, 2% FBS, while growth arrest media for AoSMC contains SM basal media, 50mg/ml gentamycin, 50 $\mu$ g/ml Amphotericin B,

0.4% FBS. Incubate at 37°C until day 2.

On day 2, serial dilutions and templates of the polypeptide of interest are designed such that they always include media controls and known-protein controls. For both stimulation and inhibition experiments, proteins are diluted in growth arrest  
5 media. For inhibition experiments, TNF $\alpha$  is added to a final concentration of 2ng/ml (NHDF) or 5ng/ml (AoSMC). Add 1/3 vol media containing controls or polypeptides of the present invention and incubate at 37°C/5% CO<sub>2</sub> until day 5.

Transfer 60 $\mu$ l from each well to another labeled 96-well plate, cover with a plate-sealer, and store at 4°C until Day 6 (for IL6 ELISA). To the remaining 100  $\mu$ l in  
10 the cell culture plate, aseptically add Alamar Blue in an amount equal to 10% of the culture volume (10 $\mu$ l). Return plates to incubator for 3 to 4 hours. Then measure fluorescence with excitation at 530nm and emission at 590nm using the CytoFluor. This yields the growth stimulation/inhibition data.

On day 5, the IL6 ELISA is performed by coating a 96 well plate with 50-100  
15  $\mu$ l/well of Anti-Human IL6 Monoclonal antibody diluted in PBS, pH 7.4, incubate ON at room temperature.

On day 6, empty the plates into the sink and blot on paper towels. Prepare Assay Buffer containing PBS with 4% BSA. Block the plates with 200  $\mu$ l/well of Pierce Super Block blocking buffer in PBS for 1-2 hr and then wash plates with wash  
20 buffer (PBS, 0.05% Tween-20). Blot plates on paper towels. Then add 50  $\mu$ l/well of diluted Anti-Human IL-6 Monoclonal, Biotin-labeled antibody at 0.50 mg/ml. Make dilutions of IL-6 stock in media (30, 10, 3, 1, 0.3, 0 ng/ml). Add duplicate samples to top row of plate. Cover the plates and incubate for 2 hours at RT on shaker. Plates are washed with wash buffer and blotted on paper towels. Dilute EU-labeled Streptavidin  
25 1:1000 in Assay buffer, and add 100  $\mu$ l/well. Cover the plate and incubate 1 h at RT. Plates are again washed with wash buffer and blotted on paper towels. Add 100  $\mu$ l/well of Enhancement Solution and shake for 5 minutes. Read the plate on the Wallac DELFIA Fluorometer. Readings from triplicate samples in each assay are tabulated and averaged.

30 A positive result in this assay suggests AoSMC cell proliferation and that the

polypeptide of the present invention may be involved in dermal fibroblast proliferation and/or smooth muscle cell proliferation. A positive result also suggests many potential uses of polypeptides, polynucleotides, agonists and/or antagonists of the polynucleotide/polypeptide of the present invention which gives a positive result.

5 For example, inflammation and immune responses, wound healing, and angiogenesis, as detailed throughout this specification. Particularly, polypeptides of the present invention and polynucleotides of the present invention may be used in wound healing and dermal regeneration, as well as the promotion of vasculogenesis, both of the blood vessels and lymphatics. The growth of vessels can be used in the treatment of,

10 for example, cardiovascular diseases. Additionally, antagonists of polypeptides and polynucleotides of the invention may be useful in treating diseases, disorders, and/or conditions which involve angiogenesis by acting as an anti-vascular (e.g., anti-angiogenesis). These diseases, disorders, and/or conditions are known in the art and/or are described herein, such as, for example, malignancies, solid tumors, benign

15 tumors, for example hemangiomas, acoustic neuromas, neurofibromas, trachomas, and pyogenic granulomas; arteriosclerotic plaques; ocular angiogenic diseases, for example, diabetic retinopathy, retinopathy of prematurity, macular degeneration, corneal graft rejection, neovascular glaucoma, retrolental fibroplasia, rubeosis, retinoblastoma, uveitis and Pterygia (abnormal blood vessel growth) of the eye;

20 rheumatoid arthritis; psoriasis; delayed wound healing; endometriosis; vasculogenesis; granulations; hypertrophic scars (keloids); nonunion fractures; scleroderma; trachoma; vascular adhesions; myocardial angiogenesis; coronary collaterals; cerebral collaterals; arteriovenous malformations; ischemic limb angiogenesis; Osler-Webber Syndrome; plaque neovascularization; telangiectasia;

25 hemophiliac joints; angiofibroma; fibromuscular dysplasia; wound granulation; Crohn's disease; and atherosclerosis. Moreover, antagonists of polypeptides and polynucleotides of the invention may be useful in treating anti-hyperproliferative diseases and/or anti-inflammatory known in the art and/or described herein.

One skilled in the art could easily modify the exemplified studies to test the

30 activity of polynucleotides (e.g., gene therapy), antibodies, agonists, and/or

antagonists and fragments and variants thereof.

*Example 45: Cellular Adhesion Molecule (CAM) Expression on Endothelial Cells*

5

The recruitment of lymphocytes to areas of inflammation and angiogenesis involves specific receptor-ligand interactions between cell surface adhesion molecules (CAMs) on lymphocytes and the vascular endothelium. The adhesion process, in both normal and pathological settings, follows a multi-step cascade that involves intercellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1), and endothelial leukocyte adhesion molecule-1 (E-selectin) expression on endothelial cells (EC). The expression of these molecules and others on the vascular endothelium determines the efficiency with which leukocytes may adhere to the local vasculature and extravasate into the local tissue during the development of an inflammatory response. The local concentration of cytokines and growth factor participate in the modulation of the expression of these CAMs.

Briefly, endothelial cells (e.g., Human Umbilical Vein Endothelial cells (HUVECs)) are grown in a standard 96 well plate to confluence, growth medium is removed from the cells and replaced with 100  $\mu$ l of 199 Medium (10% fetal bovine serum (FBS)). Samples for testing and positive or negative controls are added to the plate in triplicate (in 10  $\mu$ l volumes). Plates are then incubated at 37°C for either 5 h (selectin and integrin expression) or 24 h (integrin expression only). Plates are aspirated to remove medium and 100  $\mu$ l of 0.1% paraformaldehyde-PBS(with Ca++ and Mg++) is added to each well. Plates are held at 4°C for 30 min. Fixative is removed from the wells and wells are washed 1X with PBS(+Ca,Mg) + 0.5% BSA and drained. 10  $\mu$ l of diluted primary antibody is added to the test and control wells. Anti-ICAM-1-Biotin, Anti-VCAM-1-Biotin and Anti-E-selectin-Biotin are used at a concentration of 10  $\mu$ g/ml (1:10 dilution of 0.1 mg/ml stock antibody). Cells are incubated at 37°C for 30 min. in a humidified environment. Wells are washed three times with PBS(+Ca,Mg) + 0.5% BSA. 20  $\mu$ l of diluted ExtrAvidin-Alkaline

Phosphatase (1:5,000 dilution, referred to herein as the working dilution) are added to each well and incubated at 37°C for 30 min. Wells are washed three times with PBS(+Ca,Mg)+0.5% BSA. Dissolve 1 tablet of p-Nitrophenol Phosphate pNPP per 5 ml of glycine buffer (pH 10.4). 100 µl of pNPP substrate in glycine buffer is added to each test well. Standard wells in triplicate are prepared from the working dilution of the ExtrAvidin-Alkaline Phosphatase in glycine buffer: 1:5,000 ( $10^0$ ) >  $10^{-0.5}$  >  $10^{-1}$  >  $10^{-1.5}$ . 5 µl of each dilution is added to triplicate wells and the resulting AP content in each well is 5.50 ng, 1.74 ng, 0.55 ng, 0.18 ng. 100 µl of pNPP reagent is then added to each of the standard wells. The plate is incubated at 37°C for 4h. A volume of 50 µl of 3M NaOH is added to all wells. The plate is read on a plate reader at 405 nm using the background subtraction option on blank wells filled with glycine buffer only. Additionally, the template is set up to indicate the concentration of AP-conjugate in each standard well [ 5.50 ng; 1.74 ng; 0.55 ng; 0.18 ng]. Results are indicated as amount of bound AP-conjugate in each sample.

15

*Example 46: Alamar Blue Endothelial Cells Proliferation Assay*

This assay may be used to quantitatively determine protein mediated inhibition of bFGF-induced proliferation of Bovine Lymphatic Endothelial Cells (LECs), Bovine Aortic Endothelial Cells (BAECs) or Human Microvascular Uterine Myometrial Cells (UTMECs). This assay incorporates a fluorometric growth indicator based on detection of metabolic activity. A standard Alamar Blue Proliferation Assay is prepared in EGM-2MV with 10 ng /ml of bFGF added as a source of endothelial cell stimulation. This assay may be used with a variety of endothelial cells with slight changes in growth medium and cell concentration. Dilutions of the protein batches to be tested are diluted as appropriate. Serum-free medium (GIBCO SFM) without bFGF is used as a non-stimulated control and Angiostatin or TSP-1 are included as a known inhibitory controls.

Briefly, LEC, BAECs or UTMECs are seeded in growth media at a density of 5000 to 2000 cells/well in a 96 well plate and placed at 37-C overnight. After the

30

overnight incubation of the cells, the growth media is removed and replaced with GIBCO EC-SFM. The cells are treated with the appropriate dilutions of the protein of interest or control protein sample(s) (prepared in SFM ) in triplicate wells with additional bFGF to a concentration of 10 ng/ ml. Once the cells have been treated  
5 with the samples, the plate(s) is/are placed back in the 37° C incubator for three days. After three days 10 ml of stock alamar blue (Biosource Cat# DAL1100) is added to each well and the plate(s) is/are placed back in the 37°C incubator for four hours. The plate(s) are then read at 530nm excitation and 590nm emission using the CytoFluor fluorescence reader. Direct output is recorded in relative fluorescence units.

10 Alamar blue is an oxidation-reduction indicator that both fluoresces and changes color in response to chemical reduction of growth medium resulting from cell growth. As cells grow in culture, innate metabolic activity results in a chemical reduction of the immediate surrounding environment. Reduction related to growth causes the indicator to change from oxidized (non-fluorescent blue) form to reduced  
15 (fluorescent red) form. i.e. stimulated proliferation will produce a stronger signal and inhibited proliferation will produce a weaker signal and the total signal is proportional to the total number of cells as well as their metabolic activity. The background level of activity is observed with the starvation medium alone. This is compared to the output observed from the positive control samples (bFGF in growth medium) and  
20 protein dilutions.

*Example 47: Detection of Inhibition of a Mixed Lymphocyte Reaction*

This assay can be used to detect and evaluate inhibition of a Mixed  
25 Lymphocyte Reaction (MLR) by gene products (e.g., isolated polypeptides). Inhibition of a MLR may be due to a direct effect on cell proliferation and viability, modulation of costimulatory molecules on interacting cells, modulation of adhesiveness between lymphocytes and accessory cells, or modulation of cytokine production by accessory cells. Multiple cells may be targeted by these polypeptides



since the peripheral blood mononuclear fraction used in this assay includes T, B and natural killer lymphocytes, as well as monocytes and dendritic cells.

Polypeptides of interest found to inhibit the MLR may find application in diseases associated with lymphocyte and monocyte activation or proliferation. These  
5 include, but are not limited to, diseases such as asthma, arthritis, diabetes, inflammatory skin conditions, psoriasis, eczema, systemic lupus erythematosus, multiple sclerosis, glomerulonephritis, inflammatory bowel disease, crohn's disease, ulcerative colitis, arteriosclerosis, cirrhosis, graft vs. host disease, host vs. graft disease, hepatitis, leukemia and lymphoma.

10 Briefly, PBMCs from human donors are purified by density gradient centrifugation using Lymphocyte Separation Medium (LSM<sup>®</sup>, density 1.0770 g/ml, Organon Teknika Corporation, West Chester, PA). PBMCs from two donors are adjusted to  $2 \times 10^6$  cells/ml in RPMI-1640 (Life Technologies, Grand Island, NY) supplemented with 10% FCS and 2 mM glutamine. PBMCs from a third donor is  
15 adjusted to  $2 \times 10^5$  cells/ml. Fifty microliters of PBMCs from each donor is added to wells of a 96-well round bottom microtiter plate. Dilutions of test materials (50  $\mu$ l) is added in triplicate to microtiter wells. Test samples (of the protein of interest) are added for final dilution of 1:4; rhIL-2 (R&D Systems, Minneapolis, MN, catalog number 202-IL) is added to a final concentration of 1  $\mu$ g/ml; anti-CD4 mAb (R&D  
20 Systems, clone 34930.11, catalog number MAB379) is added to a final concentration of 10  $\mu$ g/ml. Cells are cultured for 7-8 days at 37°C in 5% CO<sub>2</sub>, and 1  $\mu$ C of [<sup>3</sup>H] thymidine is added to wells for the last 16 hrs of culture. Cells are harvested and thymidine incorporation determined using a Packard TopCount. Data is expressed as the mean and standard deviation of triplicate determinations.

25 Samples of the protein of interest are screened in separate experiments and compared to the negative control treatment, anti-CD4 mAb, which inhibits proliferation of lymphocytes and the positive control treatment, IL-2 (either as recombinant material or supernatant), which enhances proliferation of lymphocytes.

One skilled in the art could easily modify the exemplified studies to test the  
30 activity of polynucleotides (e.g., gene therapy), antibodies, agonists, and/or

antagonists and fragments and variants thereof.

It will be clear that the invention may be practiced otherwise than as particularly described in the foregoing description and examples. Numerous modifications and variations of the present invention are possible in light of the above teachings and, therefore, are within the scope of the appended claims.

The entire disclosure of each document cited (including patents, patent applications, journal articles, abstracts, laboratory manuals, books, or other disclosures) in the Background of the Invention, Detailed Description, and Examples is hereby incorporated herein by reference. Further, the hard copy of the sequence listing submitted herewith and the corresponding computer readable form are both incorporated herein by reference in their entireties. Moreover, the hard copy of and the corresponding computer readable form of the Sequence Listing of Serial No. 60/124,270 are also incorporated herein by reference in their entireties.

539

Applicant's or agent's file reference number	PA106PCT	International application	UNASSIGNED
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## INDICATIONS RELATING TO A DEPOSITED MICROORGANISM

(PCT Rule 13bis)

A. The indications made below relate to the microorganism referred to in the description on page <u>121</u> , line <u>N/A</u>	
B. IDENTIFICATION OF DEPOSIT Further deposits are identified on an additional sheet <input type="checkbox"/>	
Name of depositary institution <u>American Type Culture Collection</u>	
Address of depositary institution (including postal code and country) <u>10801 University Boulevard</u> <u>Manassas, Virginia 20110-2209</u> <u>United States of America</u>	
Date of deposit <u>20 May 1997</u>	Accession Number <u>209059</u>
C. ADDITIONAL INDICATIONS (leave blank if not applicable) This information is continued on an additional sheet <input type="checkbox"/>	
D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE (if the indications are not for all designated States)	
Europe In respect to those designations in which a European Patent is sought a sample of the deposited microorganism will be made available until the publication of the mention of the grant of the European patent or until the date on which application has been refused or withdrawn or is deemed to be withdrawn, only by the issue of such a sample to an expert nominated by the person requesting the sample (Rule 28 (4) EPC).	
E. SEPARATE FURNISHING OF INDICATIONS (leave blank if not applicable)	
The indications listed below will be submitted to the International Bureau later (specify the general nature of the indications e.g., "Accession Number of Deposit")	

For receiving Office use only	For International Bureau use only
<input checked="" type="checkbox"/> This sheet was received with the international application	<input type="checkbox"/> This sheet was received by the International Bureau on:
Authorized officer <u>John M. Powell</u> <u>PCT/Intell. Appl. Processing Div.</u> <u>(703) 305-6080</u>	Authorized officer

**ATCC Deposit No. 209059****CANADA**

The applicant requests that, until either a Canadian patent has been issued on the basis of an application or the application has been refused, or is abandoned and no longer subject to reinstatement, or is withdrawn, the Commissioner of Patents only authorizes the furnishing of a sample of the deposited biological material referred to in the application to an independent expert nominated by the Commissioner, the applicant must, by a written statement, inform the International Bureau accordingly before completion of technical preparations for publication of the international application.

**NORWAY**

The applicant hereby requests that the application has been laid open to public inspection (by the Norwegian Patent Office), or has been finally decided upon by the Norwegian Patent Office without having been laid open inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Norwegian Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Norwegian Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on the list of recognized experts drawn up by the Norwegian Patent Office or any person approved by the applicant in the individual case.

**AUSTRALIA**

The applicant hereby gives notice that the furnishing of a sample of a microorganism shall only be effected prior to the grant of a patent, or prior to the lapsing, refusal or withdrawal of the application, to a person who is a skilled addressee without an interest in the invention (Regulation 3.25(3) of the Australian Patents Regulations).

**FINLAND**

The applicant hereby requests that, until the application has been laid open to public inspection (by the National Board of Patents and Regulations), or has been finally decided upon by the National Board of Patents and Registration without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art.

**UNITED KINGDOM**

The applicant hereby requests that the furnishing of a sample of a microorganism shall only be made available to an expert. The request to this effect must be filed by the applicant with the International Bureau before the completion of the technical preparations for the international publication of the application.

Page 2

ATCC Deposit No. 209059

#### **DENMARK**

The applicant hereby requests that, until the application has been laid open to public inspection (by the Danish Patent Office), or has been finally decided upon by the Danish Patent office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Danish Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Danish Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Danish Patent Office or any person by the applicant in the individual case.

#### **SWEDEN**

The applicant hereby requests that, until the application has been laid open to public inspection (by the Swedish Patent Office), or has been finally decided upon by the Swedish Patent Office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the International Bureau before the expiration of 16 months from the priority date (preferably on the Form PCT/RO/134 reproduced in annex Z of Volume I of the PCT Applicant's Guide). If such a request has been filed by the applicant any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Swedish Patent Office or any person approved by a applicant in the individual case.

#### **NETHERLANDS**

The applicant hereby requests that until the date of a grant of a Netherlands patent or until the date on which the application is refused or withdrawn or lapsed, the microorganism shall be made available as provided in the 31F(1) of the Patent Rules only by the issue of a sample to an expert. The request to this effect must be furnished by the applicant with the Netherlands Industrial Property Office before the date on which the application is made available to the public under Section 22C or Section 25 of the Patents Act of the Kingdom of the Netherlands, whichever of the two dates occurs earlier.

542

Applicant's or agent's file reference number	PA106PCT	International application number	UNASSIGNED
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## INDICATIONS RELATING TO A DEPOSITED MICROORGANISM

(PCT Rule 13bis)

A. The indications made below relate to the microorganism referred to in the description on page <u>121</u> , line <u>N/A</u>	
B. IDENTIFICATION OF DEPOSIT Further deposits are identified on an additional sheet <input type="checkbox"/>	
Name of depositary institution American Type Culture Collection	
Address of depositary institution (including postal code and country) 10801 University Boulevard Manassas, Virginia 20110-2209 United States of America	
Date of deposit 20 May 1997	Accession Number 209060
C. ADDITIONAL INDICATIONS (leave blank if not applicable) This information is continued on an additional sheet <input type="checkbox"/>	
D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE (if the indications are not for all designated States)	
Europe In respect to those designations in which a European Patent is sought a sample of the deposited microorganism will be made available until the publication of the mention of the grant of the European patent or until the date on which application has been refused or withdrawn or is deemed to be withdrawn, only by the issue of such a sample to an expert nominated by the person requesting the sample (Rule 28 (4) EPC).	
E. SEPARATE FURNISHING OF INDICATIONS (leave blank if not applicable)	
The indications listed below will be submitted to the International Bureau later (specify the general nature of the indications e.g., "Accession Number of Deposit")	

<p>For receiving Office use only</p> <p><input checked="" type="checkbox"/> This sheet was received with the international application</p> <p>Authorized officer PCT International Processing Div. (703) 305-3030</p>	<p>For International Bureau use only</p> <p><input type="checkbox"/> This sheet was received by the International Bureau on:</p> <p>Authorized officer</p>
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**ATCC Deposit No. 209060****CANADA**

The applicant requests that, until either a Canadian patent has been issued on the basis of an application or the application has been refused, or is abandoned and no longer subject to reinstatement, or is withdrawn, the Commissioner of Patents only authorizes the furnishing of a sample of the deposited biological material referred to in the application to an independent expert nominated by the Commissioner, the applicant must, by a written statement, inform the International Bureau accordingly before completion of technical preparations for publication of the international application.

**NORWAY**

The applicant hereby requests that the application has been laid open to public inspection (by the Norwegian Patent Office), or has been finally decided upon by the Norwegian Patent Office without having been laid open inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Norwegian Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Norwegian Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on the list of recognized experts drawn up by the Norwegian Patent Office or any person approved by the applicant in the individual case.

**AUSTRALIA**

The applicant hereby gives notice that the furnishing of a sample of a microorganism shall only be effected prior to the grant of a patent, or prior to the lapsing, refusal or withdrawal of the application, to a person who is a skilled addressee without an interest in the invention (Regulation 3.25(3) of the Australian Patents Regulations).

**FINLAND**

The applicant hereby requests that, until the application has been laid open to public inspection (by the National Board of Patents and Regulations), or has been finally decided upon by the National Board of Patents and Registration without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art.

**UNITED KINGDOM**

The applicant hereby requests that the furnishing of a sample of a microorganism shall only be made available to an expert. The request to this effect must be filed by the applicant with the International Bureau before the completion of the technical preparations for the international publication of the application.

**Page 2**

**ATCC Deposit No. 209060**

### **DENMARK**

The applicant hereby requests that, until the application has been laid open to public inspection (by the Danish Patent Office), or has been finally decided upon by the Danish Patent office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Danish Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Danish Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Danish Patent Office or any person by the applicant in the individual case.

### **SWEDEN**

The applicant hereby requests that, until the application has been laid open to public inspection (by the Swedish Patent Office), or has been finally decided upon by the Swedish Patent Office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the International Bureau before the expiration of 16 months from the priority date (preferably on the Form PCT/RO/134 reproduced in annex Z of Volume I of the PCT Applicant's Guide). If such a request has been filed by the applicant any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Swedish Patent Office or any person approved by a applicant in the individual case.

### **NETHERLANDS**

The applicant hereby requests that until the date of a grant of a Netherlands patent or until the date on which the application is refused or withdrawn or lapsed, the microorganism shall be made available as provided in the 31F(1) of the Patent Rules only by the issue of a sample to an expert. The request to this effect must be furnished by the applicant with the Netherlands Industrial Property Office before the date on which the application is made available to the public under Section 22C or Section 25 of the Patents Act of the Kingdom of the Netherlands, whichever of the two dates occurs earlier.



545

Applicant's or agent's file reference number	PA106PCT	International application N°	UNASSIGNED
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## INDICATIONS RELATING TO A DEPOSITED MICROORGANISM

(PCT Rule 13bis)

<b>A.</b> The indications made below relate to the microorganism referred to in the description on page <u>121</u> , line <u>N/A</u>	
<b>B. IDENTIFICATION OF DEPOSIT</b> Further deposits are identified on an additional sheet <input type="checkbox"/>	
Name of depositary institution American Type Culture Collection	
Address of depositary institution (including postal code and country) 10801 University Boulevard Manassas, Virginia 20110-2209 United States of America	
Date of deposit 20 May 1997	Accession Number 209061
<b>C. ADDITIONAL INDICATIONS</b> (leave blank if not applicable) This information is continued on an additional sheet <input type="checkbox"/>	
<b>D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE</b> (if the indications are not for all designated States)	
Europe In respect to those designations in which a European Patent is sought a sample of the deposited microorganism will be made available until the publication of the mention of the grant of the European patent or until the date on which application has been refused or withdrawn or is deemed to be withdrawn, only by the issue of such a sample to an expert nominated by the person requesting the sample (Rule 28 (4) EPC).	
<b>E. SEPARATE FURNISHING OF INDICATIONS</b> (leave blank if not applicable)	
The indications listed below will be submitted to the International Bureau later (specify the general nature of the indications e.g., "Accession Number of Deposit")	

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**ATCC Deposit No. 209061****CANADA**

The applicant requests that, until either a Canadian patent has been issued on the basis of an application or the application has been refused, or is abandoned and no longer subject to reinstatement, or is withdrawn, the Commissioner of Patents only authorizes the furnishing of a sample of the deposited biological material referred to in the application to an independent expert nominated by the Commissioner, the applicant must, by a written statement, inform the International Bureau accordingly before completion of technical preparations for publication of the international application.

**NORWAY**

The applicant hereby requests that the application has been laid open to public inspection (by the Norwegian Patent Office), or has been finally decided upon by the Norwegian Patent Office without having been laid open inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Norwegian Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Norwegian Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on the list of recognized experts drawn up by the Norwegian Patent Office or any person approved by the applicant in the individual case.

**AUSTRALIA**

The applicant hereby gives notice that the furnishing of a sample of a microorganism shall only be effected prior to the grant of a patent, or prior to the lapsing, refusal or withdrawal of the application, to a person who is a skilled addressee without an interest in the invention (Regulation 3.25(3) of the Australian Patents Regulations).

**FINLAND**

The applicant hereby requests that, until the application has been laid open to public inspection (by the National Board of Patents and Regulations), or has been finally decided upon by the National Board of Patents and Registration without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art.

**UNITED KINGDOM**

The applicant hereby requests that the furnishing of a sample of a microorganism shall only be made available to an expert. The request to this effect must be filed by the applicant with the International Bureau before the completion of the technical preparations for the international publication of the application.

**Page 2**

**ATCC Deposit No. 209061**

## **DENMARK**

The applicant hereby requests that, until the application has been laid open to public inspection (by the Danish Patent Office), or has been finally decided upon by the Danish Patent office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Danish Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Danish Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Danish Patent Office or any person by the applicant in the individual case.

## **SWEDEN**

The applicant hereby requests that, until the application has been laid open to public inspection (by the Swedish Patent Office), or has been finally decided upon by the Swedish Patent Office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the International Bureau before the expiration of 16 months from the priority date (preferably on the Form PCT/RO/134 reproduced in annex Z of Volume I of the PCT Applicant's Guide). If such a request has been filed by the applicant any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Swedish Patent Office or any person approved by a applicant in the individual case.

## **NETHERLANDS**

The applicant hereby requests that until the date of a grant of a Netherlands patent or until the date on which the application is refused or withdrawn or lapsed, the microorganism shall be made available as provided in the 31F(1) of the Patent Rules only by the issue of a sample to an expert. The request to this effect must be furnished by the applicant with the Netherlands Industrial Property Office before the date on which the application is made available to the public under Section 22C or Section 25 of the Patents Act of the Kingdom of the Netherlands, whichever of the two dates occurs earlier.

548

Applicant's or agent's file reference number	PA106PCT	International application	UNASSIGNED
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## INDICATIONS RELATING TO A DEPOSITED MICROORGANISM

(PCT Rule 13bis)

A. The indications made below relate to the microorganism referred to in the description on page <u>121</u> , line <u>N/A</u>	
B. IDENTIFICATION OF DEPOSIT Further deposits are identified on an additional sheet <input type="checkbox"/>	
Name of depositary institution American Type Culture Collection	
Address of depositary institution (including postal code and country) 10801 University Boulevard Manassas, Virginia 20110-2209 United States of America	
Date of deposit 20 May 1997	Accession Number 209062
C. ADDITIONAL INDICATIONS (leave blank if not applicable) This information is continued on an additional sheet <input type="checkbox"/>	
D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE (if the indications are not for all designated States)	
Europe In respect to those designations in which a European Patent is sought a sample of the deposited microorganism will be made available until the publication of the mention of the grant of the European patent or until the date on which application has been refused or withdrawn or is deemed to be withdrawn, only by the issue of such a sample to an expert nominated by the person requesting the sample (Rule 28 (4) EPC).	
E. SEPARATE FURNISHING OF INDICATIONS (leave blank if not applicable)	
The indications listed below will be submitted to the International Bureau later (specify the general nature of the indications e.g., "Accession Number of Deposit")	

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Authorized officer Jaryl McDowell PCT/International Appl Processing Div. (703) 305-3639	Authorized officer

**ATCC Deposit No. 209062****CANADA**

The applicant requests that, until either a Canadian patent has been issued on the basis of an application or the application has been refused, or is abandoned and no longer subject to reinstatement, or is withdrawn, the Commissioner of Patents only authorizes the furnishing of a sample of the deposited biological material referred to in the application to an independent expert nominated by the Commissioner, the applicant must, by a written statement, inform the International Bureau accordingly before completion of technical preparations for publication of the international application.

**NORWAY**

The applicant hereby requests that the application has been laid open to public inspection (by the Norwegian Patent Office), or has been finally decided upon by the Norwegian Patent Office without having been laid open inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Norwegian Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Norwegian Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on the list of recognized experts drawn up by the Norwegian Patent Office or any person approved by the applicant in the individual case.

**AUSTRALIA**

The applicant hereby gives notice that the furnishing of a sample of a microorganism shall only be effected prior to the grant of a patent, or prior to the lapsing, refusal or withdrawal of the application, to a person who is a skilled addressee without an interest in the invention (Regulation 3.25(3) of the Australian Patents Regulations).

**FINLAND**

The applicant hereby requests that, until the application has been laid open to public inspection (by the National Board of Patents and Regulations), or has been finally decided upon by the National Board of Patents and Registration without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art.

**UNITED KINGDOM**

The applicant hereby requests that the furnishing of a sample of a microorganism shall only be made available to an expert. The request to this effect must be filed by the applicant with the International Bureau before the completion of the technical preparations for the international publication of the application.

Page 2  
ATCC Deposit No. 209062

#### **DENMARK**

The applicant hereby requests that, until the application has been laid open to public inspection (by the Danish Patent Office), or has been finally decided upon by the Danish Patent office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Danish Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Danish Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Danish Patent Office or any person by the applicant in the individual case.

#### **SWEDEN**

The applicant hereby requests that, until the application has been laid open to public inspection (by the Swedish Patent Office), or has been finally decided upon by the Swedish Patent Office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the International Bureau before the expiration of 16 months from the priority date (preferably on the Form PCT/RO/134 reproduced in annex Z of Volume I of the PCT Applicant's Guide). If such a request has been filed by the applicant any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Swedish Patent Office or any person approved by a applicant in the individual case.

#### **NETHERLANDS**

The applicant hereby requests that until the date of a grant of a Netherlands patent or until the date on which the application is refused or withdrawn or lapsed, the microorganism shall be made available as provided in the 31F(1) of the Patent Rules only by the issue of a sample to an expert. The request to this effect must be furnished by the applicant with the Netherlands Industrial Property Office before the date on which the application is made available to the public under Section 22C or Section 25 of the Patents Act of the Kingdom of the Netherlands, whichever of the two dates occurs earlier.

551

Applicant's or agent's file reference number	PA106PCT	International application?	UNASSIGNED
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## INDICATIONS RELATING TO A DEPOSITED MICROORGANISM

(PCT Rule 13bis)

<b>A.</b> The indications made below relate to the microorganism referred to in the description on page <u>121</u> , line <u>N/A</u>	
<b>B. IDENTIFICATION OF DEPOSIT</b> Further deposits are identified on an additional sheet <input type="checkbox"/>	
Name of depositary institution American Type Culture Collection	
Address of depositary institution (including postal code and country) 10801 University Boulevard Manassas, Virginia 20110-2209 United States of America	
Date of deposit 20 May 1997	Accession Number 209063
<b>C. ADDITIONAL INDICATIONS</b> (leave blank if not applicable) This information is continued on an additional sheet <input type="checkbox"/>	
<b>D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE</b> (if the indications are not for all designated States)	
Europe In respect to those designations in which a European Patent is sought a sample of the deposited microorganism will be made available until the publication of the mention of the grant of the European patent or until the date on which application has been refused or withdrawn or is deemed to be withdrawn, only by the issue of such a sample to an expert nominated by the person requesting the sample (Rule 28 (4) EPC).	
<b>E. SEPARATE FURNISHING OF INDICATIONS</b> (leave blank if not applicable)	
The indications listed below will be submitted to the International Bureau later (specify the general nature of the indications e.g., "Accession Number of Deposit")	

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**ATCC Deposit No. 209063****CANADA**

The applicant requests that, until either a Canadian patent has been issued on the basis of an application or the application has been refused, or is abandoned and no longer subject to reinstatement, or is withdrawn, the Commissioner of Patents only authorizes the furnishing of a sample of the deposited biological material referred to in the application to an independent expert nominated by the Commissioner, the applicant must, by a written statement, inform the International Bureau accordingly before completion of technical preparations for publication of the international application.

**NORWAY**

The applicant hereby requests that the application has been laid open to public inspection (by the Norwegian Patent Office), or has been finally decided upon by the Norwegian Patent Office without having been laid open inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Norwegian Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Norwegian Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on the list of recognized experts drawn up by the Norwegian Patent Office or any person approved by the applicant in the individual case.

**AUSTRALIA**

The applicant hereby gives notice that the furnishing of a sample of a microorganism shall only be effected prior to the grant of a patent, or prior to the lapsing, refusal or withdrawal of the application, to a person who is a skilled addressee without an interest in the invention (Regulation 3.25(3) of the Australian Patents Regulations).

**FINLAND**

The applicant hereby requests that, until the application has been laid open to public inspection (by the National Board of Patents and Regulations), or has been finally decided upon by the National Board of Patents and Registration without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art.

**UNITED KINGDOM**

The applicant hereby requests that the furnishing of a sample of a microorganism shall only be made available to an expert. The request to this effect must be filed by the applicant with the International Bureau before the completion of the technical preparations for the international publication of the application.



Page 2

ATCC Deposit No. 209063

## DENMARK

The applicant hereby requests that, until the application has been laid open to public inspection (by the Danish Patent Office), or has been finally decided upon by the Danish Patent office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Danish Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Danish Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Danish Patent Office or any person by the applicant in the individual case.

## SWEDEN

The applicant hereby requests that, until the application has been laid open to public inspection (by the Swedish Patent Office), or has been finally decided upon by the Swedish Patent Office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the International Bureau before the expiration of 16 months from the priority date (preferably on the Form PCT/RO/134 reproduced in annex Z of Volume I of the PCT Applicant's Guide). If such a request has been filed by the applicant any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Swedish Patent Office or any person approved by a applicant in the individual case.

## NETHERLANDS

The applicant hereby requests that until the date of a grant of a Netherlands patent or until the date on which the application is refused or withdrawn or lapsed, the microorganism shall be made available as provided in the 31F(1) of the Patent Rules only by the issue of a sample to an expert. The request to this effect must be furnished by the applicant with the Netherlands Industrial Property Office before the date on which the application is made available to the public under Section 22C or Section 25 of the Patents Act of the Kingdom of the Netherlands, whichever of the two dates occurs earlier.

554

Applicant's or agent's file reference number	PA106PCT	International application	UNASSIGNED
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## INDICATIONS RELATING TO A DEPOSITED MICROORGANISM

(PCT Rule 13bis)

A. The indications made below relate to the microorganism referred to in the description on page <u>121</u> , line <u>N/A</u>	
B. IDENTIFICATION OF DEPOSIT Further deposits are identified on an additional sheet <input type="checkbox"/>	
Name of depositary institution American Type Culture Collection	
Address of depositary institution (including postal code and country) 10801 University Boulevard Manassas, Virginia 20110-2209 United States of America	
Date of deposit 20 May 1997	Accession Number 209064
C. ADDITIONAL INDICATIONS (leave blank if not applicable) This information is continued on an additional sheet <input type="checkbox"/>	
D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE (if the indications are not for all designated States)	
Europe In respect to those designations in which a European Patent is sought a sample of the deposited microorganism will be made available until the publication of the mention of the grant of the European patent or until the date on which application has been refused or withdrawn or is deemed to be withdrawn, only by the issue of such a sample to an expert nominated by the person requesting the sample (Rule 28 (4) EPC).	
E. SEPARATE FURNISHING OF INDICATIONS (leave blank if not applicable)	
The indications listed below will be submitted to the International Bureau later (specify the general nature of the indications e.g., "Accession Number of Deposit")	

For receiving Office use only	For International Bureau use only
<input checked="" type="checkbox"/> This sheet was received with the international application	<input type="checkbox"/> This sheet was received by the International Bureau on:
Authorized officer PCT/International Processing Div. (703) 305-3639	Authorized officer

**ATCC Deposit No. 209064****CANADA**

The applicant requests that, until either a Canadian patent has been issued on the basis of an application or the application has been refused, or is abandoned and no longer subject to reinstatement, or is withdrawn, the Commissioner of Patents only authorizes the furnishing of a sample of the deposited biological material referred to in the application to an independent expert nominated by the Commissioner, the applicant must, by a written statement, inform the International Bureau accordingly before completion of technical preparations for publication of the international application.

**NORWAY**

The applicant hereby requests that the application has been laid open to public inspection (by the Norwegian Patent Office), or has been finally decided upon by the Norwegian Patent Office without having been laid open inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Norwegian Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Norwegian Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on the list of recognized experts drawn up by the Norwegian Patent Office or any person approved by the applicant in the individual case.

**AUSTRALIA**

The applicant hereby gives notice that the furnishing of a sample of a microorganism shall only be effected prior to the grant of a patent, or prior to the lapsing, refusal or withdrawal of the application, to a person who is a skilled addressee without an interest in the invention (Regulation 3.25(3) of the Australian Patents Regulations).

**FINLAND**

The applicant hereby requests that, until the application has been laid open to public inspection (by the National Board of Patents and Regulations), or has been finally decided upon by the National Board of Patents and Registration without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art.

**UNITED KINGDOM**

The applicant hereby requests that the furnishing of a sample of a microorganism shall only be made available to an expert. The request to this effect must be filed by the applicant with the International Bureau before the completion of the technical preparations for the international publication of the application.

**Page 2**

**ATCC Deposit No. 209064**

## **DENMARK**

The applicant hereby requests that, until the application has been laid open to public inspection (by the Danish Patent Office), or has been finally decided upon by the Danish Patent office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Danish Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Danish Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Danish Patent Office or any person by the applicant in the individual case.

## **SWEDEN**

The applicant hereby requests that, until the application has been laid open to public inspection (by the Swedish Patent Office), or has been finally decided upon by the Swedish Patent Office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the International Bureau before the expiration of 16 months from the priority date (preferably on the Form PCT/RO/134 reproduced in annex Z of Volume I of the PCT Applicant's Guide). If such a request has been filed by the applicant any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Swedish Patent Office or any person approved by a applicant in the individual case.

## **NETHERLANDS**

The applicant hereby requests that until the date of a grant of a Netherlands patent or until the date on which the application is refused or withdrawn or lapsed, the microorganism shall be made available as provided in the 31F(1) of the Patent Rules only by the issue of a sample to an expert. The request to this effect must be furnished by the applicant with the Netherlands Industrial Property Office before the date on which the application is made available to the public under Section 22C or Section 25 of the Patents Act of the Kingdom of the Netherlands, whichever of the two dates occurs earlier.

Applicant's or agent's file reference number	PA106PCT	International application	UNASSIGNED
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## INDICATIONS RELATING TO A DEPOSITED MICROORGANISM

(PCT Rule 13bis)

A. The indications made below relate to the microorganism referred to in the description on page <u>121</u> , line <u>N/A</u>	
B. IDENTIFICATION OF DEPOSIT Further deposits are identified on an additional sheet <input type="checkbox"/>	
Name of depositary institution American Type Culture Collection	
Address of depositary institution (including postal code and country) 10801 University Boulevard Manassas, Virginia 20110-2209 United States of America	
Date of deposit 20 May 1997	Accession Number 209065
C. ADDITIONAL INDICATIONS (leave blank if not applicable) This information is continued on an additional sheet <input type="checkbox"/>	
D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE (if the indications are not for all designated States)	
Europe In respect to those designations in which a European Patent is sought a sample of the deposited microorganism will be made available until the publication of the mention of the grant of the European patent or until the date on which application has been refused or withdrawn or is deemed to be withdrawn, only by the issue of such a sample to an expert nominated by the person requesting the sample (Rule 28 (4) EPC).	
E. SEPARATE FURNISHING OF INDICATIONS (leave blank if not applicable)	
The indications listed below will be submitted to the International Bureau later (specify the general nature of the indications e.g., "Accession Number of Deposit")	

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Authorized officer PCT/US00/05882 Processing Div. (703) 305-5639	Authorized officer

**ATCC Deposit No. 209065****CANADA**

The applicant requests that, until either a Canadian patent has been issued on the basis of an application or the application has been refused, or is abandoned and no longer subject to reinstatement, or is withdrawn, the Commissioner of Patents only authorizes the furnishing of a sample of the deposited biological material referred to in the application to an independent expert nominated by the Commissioner, the applicant must, by a written statement, inform the International Bureau accordingly before completion of technical preparations for publication of the international application.

**NORWAY**

The applicant hereby requests that the application has been laid open to public inspection (by the Norwegian Patent Office), or has been finally decided upon by the Norwegian Patent Office without having been laid open inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Norwegian Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Norwegian Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on the list of recognized experts drawn up by the Norwegian Patent Office or any person approved by the applicant in the individual case.

**AUSTRALIA**

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**FINLAND**

The applicant hereby requests that, until the application has been laid open to public inspection (by the National Board of Patents and Regulations), or has been finally decided upon by the National Board of Patents and Registration without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art.

**UNITED KINGDOM**

The applicant hereby requests that the furnishing of a sample of a microorganism shall only be made available to an expert. The request to this effect must be filed by the applicant with the International Bureau before the completion of the technical preparations for the international publication of the application.

**Page 2**  
**ATCC Deposit No. 209065**

## **DENMARK**

The applicant hereby requests that, until the application has been laid open to public inspection (by the Danish Patent Office), or has been finally decided upon by the Danish Patent office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Danish Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Danish Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Danish Patent Office or any person by the applicant in the individual case.

## **SWEDEN**

The applicant hereby requests that, until the application has been laid open to public inspection (by the Swedish Patent Office), or has been finally decided upon by the Swedish Patent Office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the International Bureau before the expiration of 16 months from the priority date (preferably on the Form PCT/RO/134 reproduced in annex Z of Volume I of the PCT Applicant's Guide). If such a request has been filed by the applicant any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Swedish Patent Office or any person approved by a applicant in the individual case.

## **NETHERLANDS**

The applicant hereby requests that until the date of a grant of a Netherlands patent or until the date on which the application is refused or withdrawn or lapsed, the microorganism shall be made available as provided in the 31F(1) of the Patent Rules only by the issue of a sample to an expert. The request to this effect must be furnished by the applicant with the Netherlands Industrial Property Office before the date on which the application is made available to the public under Section 22C or Section 25 of the Patents Act of the Kingdom of the Netherlands, whichever of the two dates occurs earlier.

560

Applicant's or agent's file reference number	PA106PCT	International application	UNASSIGNED
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## INDICATIONS RELATING TO A DEPOSITED MICROORGANISM

(PCT Rule 13bis)

A. The indications made below relate to the microorganism referred to in the description on page <u>121</u> , line <u>N/A</u>	
B. IDENTIFICATION OF DEPOSIT Further deposits are identified on an additional sheet <input type="checkbox"/>	
Name of depositary institution American Type Culture Collection	
Address of depositary institution (including postal code and country) 10801 University Boulevard Manassas, Virginia 20110-2209 United States of America	
Date of deposit 20 May 1997	Accession Number 209066
C. ADDITIONAL INDICATIONS (leave blank if not applicable) This information is continued on an additional sheet <input type="checkbox"/>	
D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE (if the indications are not for all designated States)	
Europe In respect to those designations in which a European Patent is sought a sample of the deposited microorganism will be made available until the publication of the mention of the grant of the European patent or until the date on which application has been refused or withdrawn or is deemed to be withdrawn, only by the issue of such a sample to an expert nominated by the person requesting the sample (Rule 28 (4) EPC).	
E. SEPARATE FURNISHING OF INDICATIONS (leave blank if not applicable)	
The indications listed below will be submitted to the International Bureau later (specify the general nature of the indications e.g., "Accession Number of Deposit")	

For receiving Office use only	For International Bureau use only
<input checked="" type="checkbox"/> This sheet was received with the international application	<input type="checkbox"/> This sheet was received by the International Bureau on:
Authorized officer PCT/International Processing Div. (703) 305-3639	Authorized officer



**ATCC Deposit No. 209066****CANADA**

The applicant requests that, until either a Canadian patent has been issued on the basis of an application or the application has been refused, or is abandoned and no longer subject to reinstatement, or is withdrawn, the Commissioner of Patents only authorizes the furnishing of a sample of the deposited biological material referred to in the application to an independent expert nominated by the Commissioner, the applicant must, by a written statement, inform the International Bureau accordingly before completion of technical preparations for publication of the international application.

**NORWAY**

The applicant hereby requests that the application has been laid open to public inspection (by the Norwegian Patent Office), or has been finally decided upon by the Norwegian Patent Office without having been laid open inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Norwegian Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Norwegian Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on the list of recognized experts drawn up by the Norwegian Patent Office or any person approved by the applicant in the individual case.

**AUSTRALIA**

The applicant hereby gives notice that the furnishing of a sample of a microorganism shall only be effected prior to the grant of a patent, or prior to the lapsing, refusal or withdrawal of the application, to a person who is a skilled addressee without an interest in the invention (Regulation 3.25(3) of the Australian Patents Regulations).

**FINLAND**

The applicant hereby requests that, until the application has been laid open to public inspection (by the National Board of Patents and Regulations), or has been finally decided upon by the National Board of Patents and Registration without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art.

**UNITED KINGDOM**

The applicant hereby requests that the furnishing of a sample of a microorganism shall only be made available to an expert. The request to this effect must be filed by the applicant with the International Bureau before the completion of the technical preparations for the international publication of the application.

Page 2  
ATCC Deposit No. 209066

#### **DENMARK**

The applicant hereby requests that, until the application has been laid open to public inspection (by the Danish Patent Office), or has been finally decided upon by the Danish Patent office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Danish Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Danish Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Danish Patent Office or any person by the applicant in the individual case.

#### **SWEDEN**

The applicant hereby requests that, until the application has been laid open to public inspection (by the Swedish Patent Office), or has been finally decided upon by the Swedish Patent Office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the International Bureau before the expiration of 16 months from the priority date (preferably on the Form PCT/RO/134 reproduced in annex Z of Volume I of the PCT Applicant's Guide). If such a request has been filed by the applicant any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Swedish Patent Office or any person approved by a applicant in the individual case.

#### **NETHERLANDS**

The applicant hereby requests that until the date of a grant of a Netherlands patent or until the date on which the application is refused or withdrawn or lapsed, the microorganism shall be made available as provided in the 31F(1) of the Patent Rules only by the issue of a sample to an expert. The request to this effect must be furnished by the applicant with the Netherlands Industrial Property Office before the date on which the application is made available to the public under Section 22C or Section 25 of the Patents Act of the Kingdom of the Netherlands, whichever of the two dates occurs earlier.

563

Applicant's or agent's file reference number	PA106PCT	International application number	UNASSIGNED
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## INDICATIONS RELATING TO A DEPOSITED MICROORGANISM

(PCT Rule 13bis)

A. The indications made below relate to the microorganism referred to in the description on page <u>121</u> , line <u>N/A</u>	
B. IDENTIFICATION OF DEPOSIT Further deposits are identified on an additional sheet <input type="checkbox"/>	
Name of depositary institution American Type Culture Collection	
Address of depositary institution (including postal code and country) 10801 University Boulevard Manassas, Virginia 20110-2209 United States of America	
Date of deposit 20 May 1997	Accession Number 209067
C. ADDITIONAL INDICATIONS (leave blank if not applicable) This information is continued on an additional sheet <input type="checkbox"/>	
D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE (if the indications are not for all designated States) Europe In respect to those designations in which a European Patent is sought a sample of the deposited microorganism will be made available until the publication of the mention of the grant of the European patent or until the date on which application has been refused or withdrawn or is deemed to be withdrawn, only by the issue of such a sample to an expert nominated by the person requesting the sample (Rule 28 (4) EPC).	
E. SEPARATE FURNISHING OF INDICATIONS (leave blank if not applicable) The indications listed below will be submitted to the International Bureau later (specify the general nature of the indications e.g. "Accession Number of Deposit")	

<p>For receiving Office use only</p> <p><input checked="" type="checkbox"/> This sheet was received with the international application</p> <p>Authorized officer Processing Div. (703) 665-6669</p>	<p>For International Bureau use only</p> <p><input type="checkbox"/> This sheet was received by the International Bureau on:</p> <p>Authorized officer</p>
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**ATCC Deposit No. 209067****CANADA**

The applicant requests that, until either a Canadian patent has been issued on the basis of an application or the application has been refused, or is abandoned and no longer subject to reinstatement, or is withdrawn, the Commissioner of Patents only authorizes the furnishing of a sample of the deposited biological material referred to in the application to an independent expert nominated by the Commissioner, the applicant must, by a written statement, inform the International Bureau accordingly before completion of technical preparations for publication of the international application.

**NORWAY**

The applicant hereby requests that the application has been laid open to public inspection (by the Norwegian Patent Office), or has been finally decided upon by the Norwegian Patent Office without having been laid open inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Norwegian Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Norwegian Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on the list of recognized experts drawn up by the Norwegian Patent Office or any person approved by the applicant in the individual case.

**AUSTRALIA**

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**FINLAND**

The applicant hereby requests that, until the application has been laid open to public inspection (by the National Board of Patents and Regulations), or has been finally decided upon by the National Board of Patents and Registration without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art.

**UNITED KINGDOM**

The applicant hereby requests that the furnishing of a sample of a microorganism shall only be made available to an expert. The request to this effect must be filed by the applicant with the International Bureau before the completion of the technical preparations for the international publication of the application.

**Page 2**  
**ATCC Deposit No. 209067**

#### **DENMARK**

The applicant hereby requests that, until the application has been laid open to public inspection (by the Danish Patent Office), or has been finally decided upon by the Danish Patent office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Danish Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Danish Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Danish Patent Office or any person by the applicant in the individual case.

#### **SWEDEN**

The applicant hereby requests that, until the application has been laid open to public inspection (by the Swedish Patent Office), or has been finally decided upon by the Swedish Patent Office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the International Bureau before the expiration of 16 months from the priority date (preferably on the Form PCT/RO/134 reproduced in annex Z of Volume I of the PCT Applicant's Guide). If such a request has been filed by the applicant any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Swedish Patent Office or any person approved by a applicant in the individual case.

#### **NETHERLANDS**

The applicant hereby requests that until the date of a grant of a Netherlands patent or until the date on which the application is refused or withdrawn or lapsed, the microorganism shall be made available as provided in the 31F(1) of the Patent Rules only by the issue of a sample to an expert. The request to this effect must be furnished by the applicant with the Netherlands Industrial Property Office before the date on which the application is made available to the public under Section 22C or Section 25 of the Patents Act of the Kingdom of the Netherlands, whichever of the two dates occurs earlier.

566

Applicant's or agent's file reference number	PA106PCT	International application?	UNASSIGNED
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## INDICATIONS RELATING TO A DEPOSITED MICROORGANISM

(PCT Rule 13bis)

A. The indications made below relate to the microorganism referred to in the description on page <u>121</u> , line <u>N/A</u>	
B. IDENTIFICATION OF DEPOSIT Further deposits are identified on an additional sheet <input type="checkbox"/>	
Name of depositary institution <u>American Type Culture Collection</u>	
Address of depositary institution (including postal code and country) <u>10801 University Boulevard</u> <u>Manassas, Virginia 20110-2209</u> <u>United States of America</u>	
Date of deposit <u>20 May 1997</u>	Accession Number <u>209068</u>
C. ADDITIONAL INDICATIONS (leave blank if not applicable) This information is continued on an additional sheet <input type="checkbox"/>	
D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE (if the indications are not for all designated States)	
Europe In respect to those designations in which a European Patent is sought a sample of the deposited microorganism will be made available until the publication of the mention of the grant of the European patent or until the date on which application has been refused or withdrawn or is deemed to be withdrawn, only by the issue of such a sample to an expert nominated by the person requesting the sample (Rule 28 (4) EPC).	
E. SEPARATE FURNISHING OF INDICATIONS (leave blank if not applicable)	
The indications listed below will be submitted to the International Bureau later (specify the general nature of the indications e.g., "Accession Number of Deposit")	

<p>For receiving Office use only</p> <p><input checked="" type="checkbox"/> This sheet was received with the international application</p> <p>Authorized officer PCT/International App Processing Div. (703) 305-3339</p>	<p>For International Bureau use only</p> <p><input type="checkbox"/> This sheet was received by the International Bureau on:</p> <p>Authorized officer</p>
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**ATCC Deposit No. 209068****CANADA**

The applicant requests that, until either a Canadian patent has been issued on the basis of an application or the application has been refused, or is abandoned and no longer subject to reinstatement, or is withdrawn, the Commissioner of Patents only authorizes the furnishing of a sample of the deposited biological material referred to in the application to an independent expert nominated by the Commissioner, the applicant must, by a written statement, inform the International Bureau accordingly before completion of technical preparations for publication of the international application.

**NORWAY**

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**AUSTRALIA**

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**FINLAND**

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**UNITED KINGDOM**

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Page 2

ATCC Deposit No. 209068

**DENMARK**

The applicant hereby requests that, until the application has been laid open to public inspection (by the Danish Patent Office), or has been finally decided upon by the Danish Patent office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Danish Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Danish Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Danish Patent Office or any person by the applicant in the individual case.

**SWEDEN**

The applicant hereby requests that, until the application has been laid open to public inspection (by the Swedish Patent Office), or has been finally decided upon by the Swedish Patent Office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the International Bureau before the expiration of 16 months from the priority date (preferably on the Form PCT/RO/134 reproduced in annex Z of Volume I of the PCT Applicant's Guide). If such a request has been filed by the applicant any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Swedish Patent Office or any person approved by a applicant in the individual case.

**NETHERLANDS**

The applicant hereby requests that until the date of a grant of a Netherlands patent or until the date on which the application is refused or withdrawn or lapsed, the microorganism shall be made available as provided in the 31F(1) of the Patent Rules only by the issue of a sample to an expert. The request to this effect must be furnished by the applicant with the Netherlands Industrial Property Office before the date on which the application is made available to the public under Section 22C or Section 25 of the Patents Act of the Kingdom of the Netherlands, whichever of the two dates occurs earlier.



569

Applicant's or agent's file reference number	PA106PCT	International application?	UNASSIGNED
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## INDICATIONS RELATING TO A DEPOSITED MICROORGANISM

(PCT Rule 13bis)

A. The indications made below relate to the microorganism referred to in the description on page 121, line N/A	
B. IDENTIFICATION OF DEPOSIT Further deposits are identified on an additional sheet <input type="checkbox"/>	
Name of depositary institution American Type Culture Collection	
Address of depositary institution (including postal code and country) 10801 University Boulevard Manassas, Virginia 20110-2209 United States of America	
Date of deposit 20 May 1997	Accession Number 209069
C. ADDITIONAL INDICATIONS (leave blank if not applicable) This information is continued on an additional sheet <input type="checkbox"/>	
D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE (if the indications are not for all designated States)	
Europe In respect to those designations in which a European Patent is sought a sample of the deposited microorganism will be made available until the publication of the mention of the grant of the European patent or until the date on which application has been refused or withdrawn or is deemed to be withdrawn, only by the issue of such a sample to an expert nominated by the person requesting the sample (Rule 28 (4) EPC).	
E. SEPARATE FURNISHING OF INDICATIONS (leave blank if not applicable)	
The indications listed below will be submitted to the International Bureau later (specify the general nature of the indications e.g., "Accession Number of Deposit")	

<p>For receiving Office use only</p> <p><input checked="" type="checkbox"/> This sheet was received with the international application</p> <p>Janet McDermott Authorized officer PCT/Int. Appl. Processing Div. (703) 305-3639</p>	<p>For International Bureau use only</p> <p><input type="checkbox"/> This sheet was received by the International Bureau on:</p> <p>Authorized officer</p>
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**ATCC Deposit No. 209069****CANADA**

The applicant requests that, until either a Canadian patent has been issued on the basis of an application or the application has been refused, or is abandoned and no longer subject to reinstatement, or is withdrawn, the Commissioner of Patents only authorizes the furnishing of a sample of the deposited biological material referred to in the application to an independent expert nominated by the Commissioner, the applicant must, by a written statement, inform the International Bureau accordingly before completion of technical preparations for publication of the international application.

**NORWAY**

The applicant hereby requests that the application has been laid open to public inspection (by the Norwegian Patent Office), or has been finally decided upon by the Norwegian Patent Office without having been laid open inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Norwegian Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Norwegian Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on the list of recognized experts drawn up by the Norwegian Patent Office or any person approved by the applicant in the individual case.

**AUSTRALIA**

The applicant hereby gives notice that the furnishing of a sample of a microorganism shall only be effected prior to the grant of a patent, or prior to the lapsing, refusal or withdrawal of the application, to a person who is a skilled addressee without an interest in the invention (Regulation 3.25(3) of the Australian Patents Regulations).

**FINLAND**

The applicant hereby requests that, until the application has been laid open to public inspection (by the National Board of Patents and Regulations), or has been finally decided upon by the National Board of Patents and Registration without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art.

**UNITED KINGDOM**

The applicant hereby requests that the furnishing of a sample of a microorganism shall only be made available to an expert. The request to this effect must be filed by the applicant with the International Bureau before the completion of the technical preparations for the international publication of the application.

Page 2

ATCC Deposit No. 209069

## DENMARK

The applicant hereby requests that, until the application has been laid open to public inspection (by the Danish Patent Office), or has been finally decided upon by the Danish Patent office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Danish Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Danish Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Danish Patent Office or any person by the applicant in the individual case.

## SWEDEN

The applicant hereby requests that, until the application has been laid open to public inspection (by the Swedish Patent Office), or has been finally decided upon by the Swedish Patent Office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the International Bureau before the expiration of 16 months from the priority date (preferably on the Form PCT/RO/134 reproduced in annex Z of Volume I of the PCT Applicant's Guide). If such a request has been filed by the applicant any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Swedish Patent Office or any person approved by a applicant in the individual case.

## NETHERLANDS

The applicant hereby requests that until the date of a grant of a Netherlands patent or until the date on which the application is refused or withdrawn or lapsed, the microorganism shall be made available as provided in the 31F(1) of the Patent Rules only by the issue of a sample to an expert. The request to this effect must be furnished by the applicant with the Netherlands Industrial Property Office before the date on which the application is made available to the public under Section 22C or Section 25 of the Patents Act of the Kingdom of the Netherlands, whichever of the two dates occurs earlier.

572

Applicant's or agent's file reference number	PA106PCT	International application	UNASSIGNED
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## INDICATIONS RELATING TO A DEPOSITED MICROORGANISM

(PCT Rule 13bis)

<b>A.</b> The indications made below relate to the microorganism referred to in the description on page <u>121</u> , line <u>N/A</u>	
<b>B. IDENTIFICATION OF DEPOSIT</b> Further deposits are identified on an additional sheet <input type="checkbox"/>	
Name of depositary institution American Type Culture Collection	
Address of depositary institution (including postal code and country) 10801 University Boulevard Manassas, Virginia 20110-2209 United States of America	
Date of deposit 12 January 1998	Accession Number 209579
<b>C. ADDITIONAL INDICATIONS</b> (leave blank if not applicable) This information is continued on an additional sheet <input type="checkbox"/>	
<b>D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE</b> (if the indications are not for all designated States) Europe In respect to those designations in which a European Patent is sought a sample of the deposited microorganism will be made available until the publication of the mention of the grant of the European patent or until the date on which application has been refused or withdrawn or is deemed to be withdrawn, only by the issue of such a sample to an expert nominated by the person requesting the sample (Rule 28 (4) EPC).	
<b>E. SEPARATE FURNISHING OF INDICATIONS</b> (leave blank if not applicable) The indications listed below will be submitted to the International Bureau later (specify the general nature of the indications e.g., "Accession Number of Deposit")	

<b>For receiving Office use only</b> <input checked="" type="checkbox"/> This sheet was received with the international application  Authorized officer Jon McDowell PCT/Internat'l Appl Processing Div. (703) 305-3639	<b>For International Bureau use only</b> <input type="checkbox"/> This sheet was received by the International Bureau on:  Authorized officer
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**ATCC Deposit No. 209579****CANADA**

The applicant requests that, until either a Canadian patent has been issued on the basis of an application or the application has been refused, or is abandoned and no longer subject to reinstatement, or is withdrawn, the Commissioner of Patents only authorizes the furnishing of a sample of the deposited biological material referred to in the application to an independent expert nominated by the Commissioner, the applicant must, by a written statement, inform the International Bureau accordingly before completion of technical preparations for publication of the international application.

**NORWAY**

The applicant hereby requests that the application has been laid open to public inspection (by the Norwegian Patent Office), or has been finally decided upon by the Norwegian Patent Office without having been laid open inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Norwegian Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Norwegian Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on the list of recognized experts drawn up by the Norwegian Patent Office or any person approved by the applicant in the individual case.

**AUSTRALIA**

The applicant hereby gives notice that the furnishing of a sample of a microorganism shall only be effected prior to the grant of a patent, or prior to the lapsing, refusal or withdrawal of the application, to a person who is a skilled addressee without an interest in the invention (Regulation 3.25(3) of the Australian Patents Regulations).

**FINLAND**

The applicant hereby requests that, until the application has been laid open to public inspection (by the National Board of Patents and Regulations), or has been finally decided upon by the National Board of Patents and Registration without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art.

**UNITED KINGDOM**

The applicant hereby requests that the furnishing of a sample of a microorganism shall only be made available to an expert. The request to this effect must be filed by the applicant with the International Bureau before the completion of the technical preparations for the international publication of the application.

Page 2

ATCC Deposit No. 209579

#### **DENMARK**

The applicant hereby requests that, until the application has been laid open to public inspection (by the Danish Patent Office), or has been finally decided upon by the Danish Patent office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Danish Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Danish Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Danish Patent Office or any person by the applicant in the individual case.

#### **SWEDEN**

The applicant hereby requests that, until the application has been laid open to public inspection (by the Swedish Patent Office), or has been finally decided upon by the Swedish Patent Office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the International Bureau before the expiration of 16 months from the priority date (preferably on the Form PCT/RO/134 reproduced in annex Z of Volume I of the PCT Applicant's Guide). If such a request has been filed by the applicant any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Swedish Patent Office or any person approved by a applicant in the individual case.

#### **NETHERLANDS**

The applicant hereby requests that until the date of a grant of a Netherlands patent or until the date on which the application is refused or withdrawn or lapsed, the microorganism shall be made available as provided in the 31F(1) of the Patent Rules only by the issue of a sample to an expert. The request to this effect must be furnished by the applicant with the Netherlands Industrial Property Office before the date on which the application is made available to the public under Section 22C or Section 25 of the Patents Act of the Kingdom of the Netherlands, whichever of the two dates occurs earlier.

575

Applicant's or agent's file reference number	PA106PCT	International application	UNASSIGNED
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## INDICATIONS RELATING TO A DEPOSITED MICROORGANISM

(PCT Rule 13bis)

A. The indications made below relate to the microorganism referred to in the description on page <u>121</u> , line <u>N/A</u>	
B. IDENTIFICATION OF DEPOSIT Further deposits are identified on an additional sheet <input type="checkbox"/>	
Name of depositary institution American Type Culture Collection	
Address of depositary institution (including postal code and country) 10801 University Boulevard Manassas, Virginia 20110-2209 United States of America	
Date of deposit 12 January 1998	Accession Number 209578
C. ADDITIONAL INDICATIONS (leave blank if not applicable) This information is continued on an additional sheet <input type="checkbox"/>	
D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE (if the indications are not for all designated States)	
Europe In respect to those designations in which a European Patent is sought a sample of the deposited microorganism will be made available until the publication of the mention of the grant of the European patent or until the date on which application has been refused or withdrawn or is deemed to be withdrawn, only by the issue of such a sample to an expert nominated by the person requesting the sample (Rule 28 (4) EPC).	
E. SEPARATE FURNISHING OF INDICATIONS (leave blank if not applicable)	
The indications listed below will be submitted to the International Bureau later (specify the general nature of the indications e.g., "Accession Number of Deposit")	

For receiving Office use only	For International Bureau use only
<input checked="" type="checkbox"/> This sheet was received with the international application	<input type="checkbox"/> This sheet was received by the International Bureau on:
Authorized officer Jenifer D. Brown PCT/Internal Appl Processing Div. (703) 305-8000	Authorized officer

**ATCC Deposit No. 209578****CANADA**

The applicant requests that, until either a Canadian patent has been issued on the basis of an application or the application has been refused, or is abandoned and no longer subject to reinstatement, or is withdrawn, the Commissioner of Patents only authorizes the furnishing of a sample of the deposited biological material referred to in the application to an independent expert nominated by the Commissioner, the applicant must, by a written statement, inform the International Bureau accordingly before completion of technical preparations for publication of the international application.

**NORWAY**

The applicant hereby requests that the application has been laid open to public inspection (by the Norwegian Patent Office), or has been finally decided upon by the Norwegian Patent Office without having been laid open inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Norwegian Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Norwegian Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on the list of recognized experts drawn up by the Norwegian Patent Office or any person approved by the applicant in the individual case.

**AUSTRALIA**

The applicant hereby gives notice that the furnishing of a sample of a microorganism shall only be effected prior to the grant of a patent, or prior to the lapsing, refusal or withdrawal of the application, to a person who is a skilled addressee without an interest in the invention (Regulation 3.25(3) of the Australian Patents Regulations).

**FINLAND**

The applicant hereby requests that, until the application has been laid open to public inspection (by the National Board of Patents and Regulations), or has been finally decided upon by the National Board of Patents and Registration without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art.

**UNITED KINGDOM**

The applicant hereby requests that the furnishing of a sample of a microorganism shall only be made available to an expert. The request to this effect must be filed by the applicant with the International Bureau before the completion of the technical preparations for the international publication of the application.



**Page 2**  
**ATCC Deposit No. 209578**

## **DENMARK**

The applicant hereby requests that, until the application has been laid open to public inspection (by the Danish Patent Office), or has been finally decided upon by the Danish Patent office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Danish Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Danish Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Danish Patent Office or any person by the applicant in the individual case.

## **SWEDEN**

The applicant hereby requests that, until the application has been laid open to public inspection (by the Swedish Patent Office), or has been finally decided upon by the Swedish Patent Office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the International Bureau before the expiration of 16 months from the priority date (preferably on the Form PCT/RO/134 reproduced in annex Z of Volume I of the PCT Applicant's Guide). If such a request has been filed by the applicant any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Swedish Patent Office or any person approved by a applicant in the individual case.

## **NETHERLANDS**

The applicant hereby requests that until the date of a grant of a Netherlands patent or until the date on which the application is refused or withdrawn or lapsed, the microorganism shall be made available as provided in the 31F(1) of the Patent Rules only by the issue of a sample to an expert. The request to this effect must be furnished by the applicant with the Netherlands Industrial Property Office before the date on which the application is made available to the public under Section 22C or Section 25 of the Patents Act of the Kingdom of the Netherlands, whichever of the two dates occurs earlier.

578

Applicant's or agent's file reference number	PA106PCT	International application	UNASSIGNED
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## INDICATIONS RELATING TO A DEPOSITED MICROORGANISM

(PCT Rule 13bis)

A. The indications made below relate to the microorganism referred to in the description on page <u>121</u> , line <u>N/A</u>	
B. IDENTIFICATION OF DEPOSIT Further deposits are identified on an additional sheet <input type="checkbox"/>	
Name of depositary institution American Type Culture Collection	
Address of depositary institution (including postal code and country) 10801 University Boulevard Manassas, Virginia 20110-2209 United States of America	
Date of deposit 16 July 1998	Accession Number 203067
C. ADDITIONAL INDICATIONS (leave blank if not applicable) This information is continued on an additional sheet <input type="checkbox"/>	
D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE (if the indications are not for all designated States)	
Europe In respect to those designations in which a European Patent is sought a sample of the deposited microorganism will be made available until the publication of the mention of the grant of the European patent or until the date on which application has been refused or withdrawn or is deemed to be withdrawn, only by the issue of such a sample to an expert nominated by the person requesting the sample (Rule 28 (4) EPC).	
E. SEPARATE FURNISHING OF INDICATIONS (leave blank if not applicable)	
The indications listed below will be submitted to the International Bureau later (specify the general nature of the indications e.g., "Accession Number of Deposit")	

For receiving Office use only	For International Bureau use only
<input checked="" type="checkbox"/> This sheet was received with the international application	<input type="checkbox"/> This sheet was received by the International Bureau on:
Authorized of <u>Terry McDowell</u> PCT/Internat'l Appl Processing Div. (703) 305-3663	Authorized officer

**ATCC Deposit No. 203067****CANADA**

The applicant requests that, until either a Canadian patent has been issued on the basis of an application or the application has been refused, or is abandoned and no longer subject to reinstatement, or is withdrawn, the Commissioner of Patents only authorizes the furnishing of a sample of the deposited biological material referred to in the application to an independent expert nominated by the Commissioner, the applicant must, by a written statement, inform the International Bureau accordingly before completion of technical preparations for publication of the international application.

**NORWAY**

The applicant hereby requests that the application has been laid open to public inspection (by the Norwegian Patent Office), or has been finally decided upon by the Norwegian Patent Office without having been laid open inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Norwegian Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Norwegian Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on the list of recognized experts drawn up by the Norwegian Patent Office or any person approved by the applicant in the individual case.

**AUSTRALIA**

The applicant hereby gives notice that the furnishing of a sample of a microorganism shall only be effected prior to the grant of a patent, or prior to the lapsing, refusal or withdrawal of the application, to a person who is a skilled addressee without an interest in the invention (Regulation 3.25(3) of the Australian Patents Regulations).

**FINLAND**

The applicant hereby requests that, until the application has been laid open to public inspection (by the National Board of Patents and Regulations), or has been finally decided upon by the National Board of Patents and Registration without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art.

**UNITED KINGDOM**

The applicant hereby requests that the furnishing of a sample of a microorganism shall only be made available to an expert. The request to this effect must be filed by the applicant with the International Bureau before the completion of the technical preparations for the international publication of the application.

Page 2

ATCC Deposit No. 203067

## DENMARK

The applicant hereby requests that, until the application has been laid open to public inspection (by the Danish Patent Office), or has been finally decided upon by the Danish Patent office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Danish Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Danish Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Danish Patent Office or any person by the applicant in the individual case.

## SWEDEN

The applicant hereby requests that, until the application has been laid open to public inspection (by the Swedish Patent Office), or has been finally decided upon by the Swedish Patent Office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the International Bureau before the expiration of 16 months from the priority date (preferably on the Form PCT/RO/134 reproduced in annex Z of Volume I of the PCT Applicant's Guide). If such a request has been filed by the applicant any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Swedish Patent Office or any person approved by a applicant in the individual case.

## NETHERLANDS

The applicant hereby requests that until the date of a grant of a Netherlands patent or until the date on which the application is refused or withdrawn or lapsed, the microorganism shall be made available as provided in the 31F(1) of the Patent Rules only by the issue of a sample to an expert. The request to this effect must be furnished by the applicant with the Netherlands Industrial Property Office before the date on which the application is made available to the public under Section 22C or Section 25 of the Patents Act of the Kingdom of the Netherlands, whichever of the two dates occurs earlier.

581

Applicant's or agent's file reference number	PA106PCT	International application	UNASSIGNED
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## INDICATIONS RELATING TO A DEPOSITED MICROORGANISM

(PCT Rule 13bis)

<b>A.</b> The indications made below relate to the microorganism referred to in the description on page <u>121</u> , line <u>N/A</u>	
<b>B. IDENTIFICATION OF DEPOSIT</b> Further deposits are identified on an additional sheet <input type="checkbox"/>	
Name of depositary institution <u>American Type Culture Collection</u>	
Address of depositary institution (including postal code and country) <u>10801 University Boulevard</u> <u>Manassas, Virginia 20110-2209</u> <u>United States of America</u>	
Date of deposit <u>16 July 1998</u>	Accession Number <u>203068</u>
<b>C. ADDITIONAL INDICATIONS</b> (leave blank if not applicable) This information is continued on an additional sheet <input type="checkbox"/>	
<b>D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE</b> (if the indications are not for all designated States)	
Europe In respect to those designations in which a European Patent is sought a sample of the deposited microorganism will be made available until the publication of the mention of the grant of the European patent or until the date on which application has been refused or withdrawn or is deemed to be withdrawn, only by the issue of such a sample to an expert nominated by the person requesting the sample (Rule 28 (4) EPC).	
<b>E. SEPARATE FURNISHING OF INDICATIONS</b> (leave blank if not applicable)	
The indications listed below will be submitted to the International Bureau later (specify the general nature of the indications e.g., "Accession Number of Deposit")	

For receiving Office use only <input checked="" type="checkbox"/> This sheet was received with the international application  Authorized officer <u>Joni McGowan</u> <u>PCT/Internat'l Appl Processing Div.</u> <u>(703) 305-3333</u>	For International Bureau use only <input type="checkbox"/> This sheet was received by the International Bureau on:  Authorized officer
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**ATCC Deposit No. 203068**

**CANADA**

The applicant requests that, until either a Canadian patent has been issued on the basis of an application or the application has been refused, or is abandoned and no longer subject to reinstatement, or is withdrawn, the Commissioner of Patents only authorizes the furnishing of a sample of the deposited biological material referred to in the application to an independent expert nominated by the Commissioner, the applicant must, by a written statement, inform the International Bureau accordingly before completion of technical preparations for publication of the international application.

**NORWAY**

The applicant hereby requests that the application has been laid open to public inspection (by the Norwegian Patent Office), or has been finally decided upon by the Norwegian Patent Office without having been laid open inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Norwegian Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Norwegian Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on the list of recognized experts drawn up by the Norwegian Patent Office or any person approved by the applicant in the individual case.

**AUSTRALIA**

The applicant hereby gives notice that the furnishing of a sample of a microorganism shall only be effected prior to the grant of a patent, or prior to the lapsing, refusal or withdrawal of the application, to a person who is a skilled addressee without an interest in the invention (Regulation 3.25(3) of the Australian Patents Regulations).

**FINLAND**

The applicant hereby requests that, until the application has been laid open to public inspection (by the National Board of Patents and Regulations), or has been finally decided upon by the National Board of Patents and Registration without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art.

**UNITED KINGDOM**

The applicant hereby requests that the furnishing of a sample of a microorganism shall only be made available to an expert. The request to this effect must be filed by the applicant with the International Bureau before the completion of the technical preparations for the international publication of the application.

**Page 2**

**ATCC Deposit No. 203068**

## **DENMARK**

The applicant hereby requests that, until the application has been laid open to public inspection (by the Danish Patent Office), or has been finally decided upon by the Danish Patent office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Danish Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Danish Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Danish Patent Office or any person by the applicant in the individual case.

## **SWEDEN**

The applicant hereby requests that, until the application has been laid open to public inspection (by the Swedish Patent Office), or has been finally decided upon by the Swedish Patent Office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the International Bureau before the expiration of 16 months from the priority date (preferably on the Form PCT/RO/134 reproduced in annex Z of Volume I of the PCT Applicant's Guide). If such a request has been filed by the applicant any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Swedish Patent Office or any person approved by a applicant in the individual case.

## **NETHERLANDS**

The applicant hereby requests that until the date of a grant of a Netherlands patent or until the date on which the application is refused or withdrawn or lapsed, the microorganism shall be made available as provided in the 31F(1) of the Patent Rules only by the issue of a sample to an expert. The request to this effect must be furnished by the applicant with the Netherlands Industrial Property Office before the date on which the application is made available to the public under Section 22C or Section 25 of the Patents Act of the Kingdom of the Netherlands, whichever of the two dates occurs earlier.

584

Applicant's or agent's file reference number	PA106PCT	International application	UNASSIGNED
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## INDICATIONS RELATING TO A DEPOSITED MICROORGANISM

(PCT Rule 13bis)

A. The indications made below relate to the microorganism referred to in the description on page <u>121</u> , line <u>N/A</u>	
B. IDENTIFICATION OF DEPOSIT <span style="float: right;">Further deposits are identified on an additional sheet <input type="checkbox"/></span>	
Name of depositary institution American Type Culture Collection	
Address of depositary institution (including postal code and country) 10801 University Boulevard Manassas, Virginia 20110-2209 United States of America	
Date of deposit 1 February 1999	Accession Number 203609
C. ADDITIONAL INDICATIONS (leave blank if not applicable) <span style="float: right;">This information is continued on an additional sheet <input type="checkbox"/></span>	
D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE (if the indications are not for all designated States)	
Europe In respect to those designations in which a European Patent is sought a sample of the deposited microorganism will be made available until the publication of the mention of the grant of the European patent or until the date on which application has been refused or withdrawn or is deemed to be withdrawn, only by the issue of such a sample to an expert nominated by the person requesting the sample (Rule 28 (4) EPC).	
E. SEPARATE FURNISHING OF INDICATIONS (leave blank if not applicable)	
The indications listed below will be submitted to the International Bureau later (specify the general nature of the indications e.g., "Accession Number of Deposit")	

For receiving Office use only <input checked="" type="checkbox"/> This sheet was received with the international application  Jeryl McDowell Authorized officer PCT/International Appl Processing Div. (703) 305-5339	For International Bureau use only <input type="checkbox"/> This sheet was received by the International Bureau on:  Authorized officer
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**ATCC Deposit No. 203609****CANADA**

The applicant requests that, until either a Canadian patent has been issued on the basis of an application or the application has been refused, or is abandoned and no longer subject to reinstatement, or is withdrawn, the Commissioner of Patents only authorizes the furnishing of a sample of the deposited biological material referred to in the application to an independent expert nominated by the Commissioner, the applicant must, by a written statement, inform the International Bureau accordingly before completion of technical preparations for publication of the international application.

**NORWAY**

The applicant hereby requests that the application has been laid open to public inspection (by the Norwegian Patent Office), or has been finally decided upon by the Norwegian Patent Office without having been laid open inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Norwegian Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Norwegian Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on the list of recognized experts drawn up by the Norwegian Patent Office or any person approved by the applicant in the individual case.

**AUSTRALIA**

The applicant hereby gives notice that the furnishing of a sample of a microorganism shall only be effected prior to the grant of a patent, or prior to the lapsing, refusal or withdrawal of the application, to a person who is a skilled addressee without an interest in the invention (Regulation 3.25(3) of the Australian Patents Regulations).

**FINLAND**

The applicant hereby requests that, until the application has been laid open to public inspection (by the National Board of Patents and Regulations), or has been finally decided upon by the National Board of Patents and Registration without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art.

**UNITED KINGDOM**

The applicant hereby requests that the furnishing of a sample of a microorganism shall only be made available to an expert. The request to this effect must be filed by the applicant with the International Bureau before the completion of the technical preparations for the international publication of the application.

**Page 2****ATCC Deposit No. 203609****DENMARK**

The applicant hereby requests that, until the application has been laid open to public inspection (by the Danish Patent Office), or has been finally decided upon by the Danish Patent office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Danish Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Danish Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Danish Patent Office or any person by the applicant in the individual case.

**SWEDEN**

The applicant hereby requests that, until the application has been laid open to public inspection (by the Swedish Patent Office), or has been finally decided upon by the Swedish Patent Office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the International Bureau before the expiration of 16 months from the priority date (preferably on the Form PCT/RO/134 reproduced in annex Z of Volume I of the PCT Applicant's Guide). If such a request has been filed by the applicant any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Swedish Patent Office or any person approved by a applicant in the individual case.

**NETHERLANDS**

The applicant hereby requests that until the date of a grant of a Netherlands patent or until the date on which the application is refused or withdrawn or lapsed, the microorganism shall be made available as provided in the 31F(1) of the Patent Rules only by the issue of a sample to an expert. The request to this effect must be furnished by the applicant with the Netherlands Industrial Property Office before the date on which the application is made available to the public under Section 22C or Section 25 of the Patents Act of the Kingdom of the Netherlands, whichever of the two dates occurs earlier.

587

Applicant's or agent's file reference number	PA106PCT	International application	UNASSIGNED
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## INDICATIONS RELATING TO A DEPOSITED MICROORGANISM

(PCT Rule 13bis)

A. The indications made below relate to the microorganism referred to in the description on page <u>121</u> , line <u>N/A</u>	
B. IDENTIFICATION OF DEPOSIT Further deposits are identified on an additional sheet <input type="checkbox"/>	
Name of depositary institution American Type Culture Collection	
Address of depositary institution (including postal code and country) 10801 University Boulevard Manassas, Virginia 20110-2209 United States of America	
Date of deposit 1 February 1999	Accession Number 203610
C. ADDITIONAL INDICATIONS (leave blank if not applicable) This information is continued on an additional sheet <input type="checkbox"/>	
D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE (if the indications are not for all designated States)	
Europe In respect to those designations in which a European Patent is sought a sample of the deposited microorganism will be made available until the publication of the mention of the grant of the European patent or until the date on which application has been refused or withdrawn or is deemed to be withdrawn, only by the issue of such a sample to an expert nominated by the person requesting the sample (Rule 28 (4) EPC).	
E. SEPARATE FURNISHING OF INDICATIONS (leave blank if not applicable)	
The indications listed below will be submitted to the International Bureau later (specify the general nature of the indications e.g., "Accession Number of Deposit")	

For receiving Office use only	For International Bureau use only
<input checked="" type="checkbox"/> This sheet was received with the international application	<input type="checkbox"/> This sheet was received by the International Bureau on:
Jerry L. Carroll Authorized officer PCT/International Appl Processing Div. (703) 305-6639	Authorized officer

**ATCC Deposit No. 203610****CANADA**

The applicant requests that, until either a Canadian patent has been issued on the basis of an application or the application has been refused, or is abandoned and no longer subject to reinstatement, or is withdrawn, the Commissioner of Patents only authorizes the furnishing of a sample of the deposited biological material referred to in the application to an independent expert nominated by the Commissioner, the applicant must, by a written statement, inform the International Bureau accordingly before completion of technical preparations for publication of the international application.

**NORWAY**

The applicant hereby requests that the application has been laid open to public inspection (by the Norwegian Patent Office), or has been finally decided upon by the Norwegian Patent Office without having been laid open inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Norwegian Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Norwegian Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on the list of recognized experts drawn up by the Norwegian Patent Office or any person approved by the applicant in the individual case.

**AUSTRALIA**

The applicant hereby gives notice that the furnishing of a sample of a microorganism shall only be effected prior to the grant of a patent, or prior to the lapsing, refusal or withdrawal of the application, to a person who is a skilled addressee without an interest in the invention (Regulation 3.25(3) of the Australian Patents Regulations).

**FINLAND**

The applicant hereby requests that, until the application has been laid open to public inspection (by the National Board of Patents and Regulations), or has been finally decided upon by the National Board of Patents and Registration without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art.

**UNITED KINGDOM**

The applicant hereby requests that the furnishing of a sample of a microorganism shall only be made available to an expert. The request to this effect must be filed by the applicant with the International Bureau before the completion of the technical preparations for the international publication of the application.

Page 2

ATCC Deposit No. 203610

#### **DENMARK**

The applicant hereby requests that, until the application has been laid open to public inspection (by the Danish Patent Office), or has been finally decided upon by the Danish Patent office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Danish Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Danish Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Danish Patent Office or any person by the applicant in the individual case.

#### **SWEDEN**

The applicant hereby requests that, until the application has been laid open to public inspection (by the Swedish Patent Office), or has been finally decided upon by the Swedish Patent Office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the International Bureau before the expiration of 16 months from the priority date (preferably on the Form PCT/RO/134 reproduced in annex Z of Volume I of the PCT Applicant's Guide). If such a request has been filed by the applicant any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Swedish Patent Office or any person approved by a applicant in the individual case.

#### **NETHERLANDS**

The applicant hereby requests that until the date of a grant of a Netherlands patent or until the date on which the application is refused or withdrawn or lapsed, the microorganism shall be made available as provided in the 31F(1) of the Patent Rules only by the issue of a sample to an expert. The request to this effect must be furnished by the applicant with the Netherlands Industrial Property Office before the date on which the application is made available to the public under Section 22C or Section 25 of the Patents Act of the Kingdom of the Netherlands, whichever of the two dates occurs earlier.

590

Applicant's or agent's file reference number	PA106PCT	International application	UNASSIGNED
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## INDICATIONS RELATING TO A DEPOSITED MICROORGANISM

(PCT Rule 13bis)

A. The indications made below relate to the microorganism referred to in the description on page <u>121</u> , line <u>N/A</u>	
B. IDENTIFICATION OF DEPOSIT Further deposits are identified on an additional sheet <input type="checkbox"/>	
Name of depositary institution American Type Culture Collection	
Address of depositary institution (including postal code and country) 10801 University Boulevard Manassas, Virginia 20110-2209 United States of America	
Date of deposit 17 November 1998	Accession Number 203485
C. ADDITIONAL INDICATIONS (leave blank if not applicable) This information is continued on an additional sheet <input type="checkbox"/>	
D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE (if the indications are not for all designated States)	
Europe In respect to those designations in which a European Patent is sought a sample of the deposited microorganism will be made available until the publication of the mention of the grant of the European patent or until the date on which application has been refused or withdrawn or is deemed to be withdrawn, only by the issue of such a sample to an expert nominated by the person requesting the sample (Rule 28 (4) EPC).	
E. SEPARATE FURNISHING OF INDICATIONS (leave blank if not applicable)	
The indications listed below will be submitted to the International Bureau later (specify the general nature of the indications e.g., "Accession Number of Deposit")	

For receiving Office use only	For International Bureau use only
<input checked="" type="checkbox"/> This sheet was received with the international application	<input type="checkbox"/> This sheet was received by the International Bureau on:
Authorized officer PCT/Int'l Appl Processing Div. (703) 305-3639	Authorized officer

**ATCC Deposit No. 203485****CANADA**

The applicant requests that, until either a Canadian patent has been issued on the basis of an application or the application has been refused, or is abandoned and no longer subject to reinstatement; or is withdrawn, the Commissioner of Patents only authorizes the furnishing of a sample of the deposited biological material referred to in the application to an independent expert nominated by the Commissioner, the applicant must, by a written statement, inform the International Bureau accordingly before completion of technical preparations for publication of the international application.

**NORWAY**

The applicant hereby requests that the application has been laid open to public inspection (by the Norwegian Patent Office), or has been finally decided upon by the Norwegian Patent Office without having been laid open inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Norwegian Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Norwegian Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on the list of recognized experts drawn up by the Norwegian Patent Office or any person approved by the applicant in the individual case.

**AUSTRALIA**

The applicant hereby gives notice that the furnishing of a sample of a microorganism shall only be effected prior to the grant of a patent, or prior to the lapsing, refusal or withdrawal of the application, to a person who is a skilled addressee without an interest in the invention (Regulation 3.25(3) of the Australian Patents Regulations).

**FINLAND**

The applicant hereby requests that, until the application has been laid open to public inspection (by the National Board of Patents and Regulations), or has been finally decided upon by the National Board of Patents and Registration without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art.

**UNITED KINGDOM**

The applicant hereby requests that the furnishing of a sample of a microorganism shall only be made available to an expert. The request to this effect must be filed by the applicant with the International Bureau before the completion of the technical preparations for the international publication of the application.

**Page 2**

**ATCC Deposit No. 203485**

### **DENMARK**

The applicant hereby requests that, until the application has been laid open to public inspection (by the Danish Patent Office), or has been finally decided upon by the Danish Patent office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Danish Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Danish Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Danish Patent Office or any person by the applicant in the individual case.

### **SWEDEN**

The applicant hereby requests that, until the application has been laid open to public inspection (by the Swedish Patent Office), or has been finally decided upon by the Swedish Patent Office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the International Bureau before the expiration of 16 months from the priority date (preferably on the Form PCT/RO/134 reproduced in annex Z of Volume I of the PCT Applicant's Guide). If such a request has been filed by the applicant any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Swedish Patent Office or any person approved by a applicant in the individual case.

### **NETHERLANDS**

The applicant hereby requests that until the date of a grant of a Netherlands patent or until the date on which the application is refused or withdrawn or lapsed, the microorganism shall be made available as provided in the 31F(1) of the Patent Rules only by the issue of a sample to an expert. The request to this effect must be furnished by the applicant with the Netherlands Industrial Property Office before the date on which the application is made available to the public under Section 22C or Section 25 of the Patents Act of the Kingdom of the Netherlands, whichever of the two dates occurs earlier.



593

Applicant's or agent's file reference number	PA106PCT	International application	UNASSIGNED
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## INDICATIONS RELATING TO A DEPOSITED MICROORGANISM

(PCT Rule 13bis)

A. The indications made below relate to the microorganism referred to in the description on page <u>121</u> , line <u>N/A</u>	
B. IDENTIFICATION OF DEPOSIT Further deposits are identified on an additional sheet <input type="checkbox"/>	
Name of depositary institution American Type Culture Collection	
Address of depositary institution (including postal code and country) 10801 University Boulevard Manassas, Virginia 20110-2209 United States of America	
Date of deposit 18 June 1999	Accession Number PTA-252
C. ADDITIONAL INDICATIONS (leave blank if not applicable) This information is continued on an additional sheet <input type="checkbox"/>	
D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE (if the indications are not for all designated States)	
Europe In respect to those designations in which a European Patent is sought a sample of the deposited microorganism will be made available until the publication of the mention of the grant of the European patent or until the date on which application has been refused or withdrawn or is deemed to be withdrawn, only by the issue of such a sample to an expert nominated by the person requesting the sample (Rule 28 (4) EPC).	
E. SEPARATE FURNISHING OF INDICATIONS (leave blank if not applicable)	
The indications listed below will be submitted to the International Bureau later (specify the general nature of the indications e.g., "Accession Number of Deposit")	

<p>For receiving Office use only</p> <p><input checked="" type="checkbox"/> This sheet was received with the international application</p> <p>Authorized officer Jeryl McDowell PCT/Internat'l Appl Processing Div. (703) 305-3839</p>	<p>For International Bureau use only</p> <p><input type="checkbox"/> This sheet was received by the International Bureau on:</p> <p>Authorized officer</p>
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**ATCC Deposit No. PTA-252****CANADA**

The applicant requests that, until either a Canadian patent has been issued on the basis of an application or the application has been refused, or is abandoned and no longer subject to reinstatement, or is withdrawn, the Commissioner of Patents only authorizes the furnishing of a sample of the deposited biological material referred to in the application to an independent expert nominated by the Commissioner, the applicant must, by a written statement, inform the International Bureau accordingly before completion of technical preparations for publication of the international application.

**NORWAY**

The applicant hereby requests that the application has been laid open to public inspection (by the Norwegian Patent Office), or has been finally decided upon by the Norwegian Patent Office without having been laid open inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Norwegian Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Norwegian Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on the list of recognized experts drawn up by the Norwegian Patent Office or any person approved by the applicant in the individual case.

**AUSTRALIA**

The applicant hereby gives notice that the furnishing of a sample of a microorganism shall only be effected prior to the grant of a patent, or prior to the lapsing, refusal or withdrawal of the application, to a person who is a skilled addressee without an interest in the invention (Regulation 3.25(3) of the Australian Patents Regulations).

**FINLAND**

The applicant hereby requests that, until the application has been laid open to public inspection (by the National Board of Patents and Regulations), or has been finally decided upon by the National Board of Patents and Registration without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art.

**UNITED KINGDOM**

The applicant hereby requests that the furnishing of a sample of a microorganism shall only be made available to an expert. The request to this effect must be filed by the applicant with the International Bureau before the completion of the technical preparations for the international publication of the application.

Page 2

ATCC Deposit No. PTA-252

#### **DENMARK**

The applicant hereby requests that, until the application has been laid open to public inspection (by the Danish Patent Office), or has been finally decided upon by the Danish Patent office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Danish Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Danish Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Danish Patent Office or any person by the applicant in the individual case.

#### **SWEDEN**

The applicant hereby requests that, until the application has been laid open to public inspection (by the Swedish Patent Office), or has been finally decided upon by the Swedish Patent Office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the International Bureau before the expiration of 16 months from the priority date (preferably on the Form PCT/RO/134 reproduced in annex Z of Volume I of the PCT Applicant's Guide). If such a request has been filed by the applicant any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Swedish Patent Office or any person approved by a applicant in the individual case.

#### **NETHERLANDS**

The applicant hereby requests that until the date of a grant of a Netherlands patent or until the date on which the application is refused or withdrawn or lapsed, the microorganism shall be made available as provided in the 31F(1) of the Patent Rules only by the issue of a sample to an expert. The request to this effect must be furnished by the applicant with the Netherlands Industrial Property Office before the date on which the application is made available to the public under Section 22C or Section 25 of the Patents Act of the Kingdom of the Netherlands, whichever of the two dates occurs earlier.

596

Applicant's or agent's file reference number	PA106PCT	International application	UNASSIGNED
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## INDICATIONS RELATING TO A DEPOSITED MICROORGANISM

(PCT Rule 13bis)

A. The indications made below relate to the microorganism referred to in the description on page <u>121</u> , line <u>N/A</u>	
B. IDENTIFICATION OF DEPOSIT Further deposits are identified on an additional sheet <input type="checkbox"/>	
Name of depositary institution American Type Culture Collection	
Address of depositary institution (including postal code and country) 10801 University Boulevard Manassas, Virginia 20110-2209 United States of America	
Date of deposit 18 June 1999	Accession Number PTA-253
C. ADDITIONAL INDICATIONS (leave blank if not applicable) This information is continued on an additional sheet <input type="checkbox"/>	
D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE (if the indications are not for all designated States)	
Europe In respect to those designations in which a European Patent is sought a sample of the deposited microorganism will be made available until the publication of the mention of the grant of the European patent or until the date on which application has been refused or withdrawn or is deemed to be withdrawn, only by the issue of such a sample to an expert nominated by the person requesting the sample (Rule 28 (4) EPC).	
E. SEPARATE FURNISHING OF INDICATIONS (leave blank if not applicable)	
The indications listed below will be submitted to the International Bureau later (specify the general nature of the indications e.g., "Accession Number of Deposit")	

<p>For receiving Office use only</p> <p><input checked="" type="checkbox"/> This sheet was received with the international application</p> <p>Jeryl McDowell Authorized officer PCT/US00/05882 Appl Processing Div. (703) 305-5639</p>	<p>For International Bureau use only</p> <p><input type="checkbox"/> This sheet was received by the International Bureau on:</p> <p>Authorized officer</p>
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**ATCC Deposit No. PTA-253****CANADA**

The applicant requests that, until either a Canadian patent has been issued on the basis of an application or the application has been refused, or is abandoned and no longer subject to reinstatement, or is withdrawn, the Commissioner of Patents only authorizes the furnishing of a sample of the deposited biological material referred to in the application to an independent expert nominated by the Commissioner, the applicant must, by a written statement, inform the International Bureau accordingly before completion of technical preparations for publication of the international application.

**NORWAY**

The applicant hereby requests that the application has been laid open to public inspection (by the Norwegian Patent Office), or has been finally decided upon by the Norwegian Patent Office without having been laid open inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Norwegian Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Norwegian Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on the list of recognized experts drawn up by the Norwegian Patent Office or any person approved by the applicant in the individual case.

**AUSTRALIA**

The applicant hereby gives notice that the furnishing of a sample of a microorganism shall only be effected prior to the grant of a patent, or prior to the lapsing, refusal or withdrawal of the application, to a person who is a skilled addressee without an interest in the invention (Regulation 3.25(3) of the Australian Patents Regulations).

**FINLAND**

The applicant hereby requests that, until the application has been laid open to public inspection (by the National Board of Patents and Regulations), or has been finally decided upon by the National Board of Patents and Registration without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art.

**UNITED KINGDOM**

The applicant hereby requests that the furnishing of a sample of a microorganism shall only be made available to an expert. The request to this effect must be filed by the applicant with the International Bureau before the completion of the technical preparations for the international publication of the application.

**Page 2****ATCC Deposit No. PTA-253****DENMARK**

The applicant hereby requests that, until the application has been laid open to public inspection (by the Danish Patent Office), or has been finally decided upon by the Danish Patent office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Danish Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Danish Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Danish Patent Office or any person by the applicant in the individual case.

**SWEDEN**

The applicant hereby requests that, until the application has been laid open to public inspection (by the Swedish Patent Office), or has been finally decided upon by the Swedish Patent Office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the International Bureau before the expiration of 16 months from the priority date (preferably on the Form PCT/RO/134 reproduced in annex Z of Volume I of the PCT Applicant's Guide). If such a request has been filed by the applicant any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Swedish Patent Office or any person approved by a applicant in the individual case.

**NETHERLANDS**

The applicant hereby requests that until the date of a grant of a Netherlands patent or until the date on which the application is refused or withdrawn or lapsed, the microorganism shall be made available as provided in the 31F(1) of the Patent Rules only by the issue of a sample to an expert. The request to this effect must be furnished by the applicant with the Netherlands Industrial Property Office before the date on which the application is made available to the public under Section 22C or Section 25 of the Patents Act of the Kingdom of the Netherlands, whichever of the two dates occurs earlier.

599

Applicant's or agent's file reference number	PA106PCT	International application	UNASSIGNED
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## INDICATIONS RELATING TO A DEPOSITED MICROORGANISM

(PCT Rule 13bis)

A. The indications made below relate to the microorganism referred to in the description on page <u>121</u> , line <u>N/A</u>	
B. IDENTIFICATION OF DEPOSIT Further deposits are identified on an additional sheet <input type="checkbox"/>	
Name of depositary institution American Type Culture Collection	
Address of depositary institution (including postal code and country) 10801 University Boulevard Manassas, Virginia 20110-2209 United States of America	
Date of deposit 22 December 1999	Accession Number PTA-1081
C. ADDITIONAL INDICATIONS (leave blank if not applicable) This information is continued on an additional sheet <input type="checkbox"/>	
D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE (if the indications are not for all designated States) Europe In respect to those designations in which a European Patent is sought a sample of the deposited microorganism will be made available until the publication of the mention of the grant of the European patent or until the date on which application has been refused or withdrawn or is deemed to be withdrawn, only by the issue of such a sample to an expert nominated by the person requesting the sample (Rule 28 (4) EPC).	
E. SEPARATE FURNISHING OF INDICATIONS (leave blank if not applicable) The indications listed below will be submitted to the International Bureau later (specify the general nature of the indications e.g., "Accession Number of Deposit")	

For receiving Office use only <input checked="" type="checkbox"/> This sheet was received with the international application  Authorized officer PCT/International Appl Processing Div. (703) 305-3639	For International Bureau use only <input type="checkbox"/> This sheet was received by the International Bureau on:  Authorized officer
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**ATCC Deposit No. PTA-1081****CANADA**

The applicant requests that, until either a Canadian patent has been issued on the basis of an application or the application has been refused, or is abandoned and no longer subject to reinstatement, or is withdrawn, the Commissioner of Patents only authorizes the furnishing of a sample of the deposited biological material referred to in the application to an independent expert nominated by the Commissioner, the applicant must, by a written statement, inform the International Bureau accordingly before completion of technical preparations for publication of the international application.

**NORWAY**

The applicant hereby requests that the application has been laid open to public inspection (by the Norwegian Patent Office), or has been finally decided upon by the Norwegian Patent Office without having been laid open inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Norwegian Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Norwegian Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on the list of recognized experts drawn up by the Norwegian Patent Office or any person approved by the applicant in the individual case.

**AUSTRALIA**

The applicant hereby gives notice that the furnishing of a sample of a microorganism shall only be effected prior to the grant of a patent, or prior to the lapsing, refusal or withdrawal of the application, to a person who is a skilled addressee without an interest in the invention (Regulation 3.25(3) of the Australian Patents Regulations).

**FINLAND**

The applicant hereby requests that, until the application has been laid open to public inspection (by the National Board of Patents and Regulations), or has been finally decided upon by the National Board of Patents and Registration without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art.

**UNITED KINGDOM**

The applicant hereby requests that the furnishing of a sample of a microorganism shall only be made available to an expert. The request to this effect must be filed by the applicant with the International Bureau before the completion of the technical preparations for the international publication of the application.



**Page 2**

**ATCC Deposit No. PTA-1081**

### **DENMARK**

The applicant hereby requests that, until the application has been laid open to public inspection (by the Danish Patent Office), or has been finally decided upon by the Danish Patent office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Danish Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Danish Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Danish Patent Office or any person by the applicant in the individual case.

### **SWEDEN**

The applicant hereby requests that, until the application has been laid open to public inspection (by the Swedish Patent Office), or has been finally decided upon by the Swedish Patent Office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the International Bureau before the expiration of 16 months from the priority date (preferably on the Form PCT/RO/134 reproduced in annex Z of Volume I of the PCT Applicant's Guide). If such a request has been filed by the applicant any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Swedish Patent Office or any person approved by a applicant in the individual case.

### **NETHERLANDS**

The applicant hereby requests that until the date of a grant of a Netherlands patent or until the date on which the application is refused or withdrawn or lapsed, the microorganism shall be made available as provided in the 31F(1) of the Patent Rules only by the issue of a sample to an expert. The request to this effect must be furnished by the applicant with the Netherlands Industrial Property Office before the date on which the application is made available to the public under Section 22C or Section 25 of the Patents Act of the Kingdom of the Netherlands, whichever of the two dates occurs earlier.

*What Is Claimed Is:*

1. An isolated nucleic acid molecule comprising a polynucleotide having a nucleotide sequence at least 95% identical to a sequence selected from the group consisting of:
  - (a) a polynucleotide fragment of SEQ ID NO:X or a polynucleotide fragment of the cDNA sequence included in the related cDNA clone, which is hybridizable to SEQ ID NO:X;
  - (b) a polynucleotide encoding a polypeptide fragment of SEQ ID NO:Y or a polypeptide fragment encoded by the cDNA sequence included in the related cDNA clone, which is hybridizable to SEQ ID NO:X;
  - (c) a polynucleotide encoding a polypeptide fragment of a polypeptide encoded by SEQ ID NO:X or a polypeptide fragment encoded by the cDNA sequence included in the related cDNA clone, which is hybridizable to SEQ ID NO:X;
  - (d) a polynucleotide encoding a polypeptide domain of SEQ ID NO:Y or a polypeptide domain encoded by the cDNA sequence included in the related cDNA clone, which is hybridizable to SEQ ID NO:X;
  - (e) a polynucleotide encoding a polypeptide epitope of SEQ ID NO:Y or a polypeptide epitope encoded by the cDNA sequence included in the related cDNA clone, which is hybridizable to SEQ ID NO:X;
  - (f) a polynucleotide encoding a polypeptide of SEQ ID NO:Y or the cDNA sequence included in the related cDNA clone, which is hybridizable to SEQ ID NO:X, having biological activity;
  - (g) a polynucleotide which is a variant of SEQ ID NO:X;
  - (h) a polynucleotide which is an allelic variant of SEQ ID NO:X;
  - (i) a polynucleotide which encodes a species homologue of the SEQ ID NO:Y;
  - (j) a polynucleotide capable of hybridizing under stringent conditions to any one of the polynucleotides specified in (a)-(i), wherein said polynucleotide does not hybridize under stringent conditions to a nucleic acid molecule having a nucleotide

sequence of only A residues or of only T residues.

2. The isolated nucleic acid molecule of claim 1, wherein the polynucleotide fragment comprises a nucleotide sequence encoding a protein.

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3. The isolated nucleic acid molecule of claim 1, wherein the polynucleotide fragment comprises a nucleotide sequence encoding the sequence identified as SEQ ID NO:Y or the polypeptide encoded by the cDNA sequence included in the related cDNA clone, which is hybridizable to SEQ ID NO:X.

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4. The isolated nucleic acid molecule of claim 1, wherein the polynucleotide fragment comprises the entire nucleotide sequence of SEQ ID NO:X or the cDNA sequence included in the related cDNA clone, which is hybridizable to SEQ ID NO:X.

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5. The isolated nucleic acid molecule of claim 2, wherein the nucleotide sequence comprises sequential nucleotide deletions from either the C-terminus or the N-terminus.

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6. The isolated nucleic acid molecule of claim 3, wherein the nucleotide sequence comprises sequential nucleotide deletions from either the C-terminus or the N-terminus.

25

7. A recombinant vector comprising the isolated nucleic acid molecule of claim 1.

8. A method of making a recombinant host cell comprising the isolated nucleic acid molecule of claim 1.

30

9. A recombinant host cell produced by the method of claim 8.

10. The recombinant host cell of claim 9 comprising vector sequences.
11. An isolated polypeptide comprising an amino acid sequence at least  
5 95% identical to a sequence selected from the group consisting of:
- (a) a polypeptide fragment of SEQ ID NO:Y or of the sequence encoded by the cDNA included in the related cDNA clone;
  - (b) a polypeptide fragment of SEQ ID NO:Y or of the sequence encoded by the cDNA included in the related cDNA clone, having biological activity;
  - 10 (c) a polypeptide domain of SEQ ID NO:Y or of the sequence encoded by the cDNA included in the related cDNA clone;
  - (d) a polypeptide epitope of SEQ ID NO:Y or of the sequence encoded by the cDNA included in the related cDNA clone;
  - (e) a full length protein of SEQ ID NO:Y or of the sequence encoded by the  
15 cDNA included in the related cDNA clone;
  - (f) a variant of SEQ ID NO:Y;
  - (g) an allelic variant of SEQ ID NO:Y; or
  - (h) a species homologue of the SEQ ID NO:Y.
- 20 12. The isolated polypeptide of claim 11, wherein the full length protein comprises sequential amino acid deletions from either the C-terminus or the N-terminus.
13. An isolated antibody that binds specifically to the isolated polypeptide  
25 of claim 11.
14. A recombinant host cell that expresses the isolated polypeptide of claim 11.
- 30 15. A method of making an isolated polypeptide comprising:

(a) culturing the recombinant host cell of claim 14 under conditions such that said polypeptide is expressed; and

(b) recovering said polypeptide.

5           16.     The polypeptide produced by claim 15.

17.     A method for preventing, treating, or ameliorating a medical condition, comprising administering to a mammalian subject a therapeutically effective amount of the polypeptide of claim 11 or the polynucleotide of claim 1.

10

18.     A method of diagnosing a pathological condition or a susceptibility to a pathological condition in a subject comprising:

(a) determining the presence or absence of a mutation in the polynucleotide of claim 1; and

15           (b) diagnosing a pathological condition or a susceptibility to a pathological condition based on the presence or absence of said mutation.

19.     A method of diagnosing a pathological condition or a susceptibility to a pathological condition in a subject comprising:

20           (a) determining the presence or amount of expression of the polypeptide of claim 11 in a biological sample; and

(b) diagnosing a pathological condition or a susceptibility to a pathological condition based on the presence or amount of expression of the polypeptide.

25           20.     A method for identifying a binding partner to the polypeptide of claim 11 comprising:

(a) contacting the polypeptide of claim 11 with a binding partner; and

(b) determining whether the binding partner effects an activity of the polypeptide.

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21. The gene corresponding to the cDNA sequence of SEQ ID NO:Y.
22. A method of identifying an activity in a biological assay, wherein the method comprises:
- 5 (a) expressing SEQ ID NO:X in a cell;
- (b) isolating the supernatant;
- (c) detecting an activity in a biological assay; and
- (d) identifying the protein in the supernatant having the activity.
- 10 23. The product produced by the method of claim 20.

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